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The Western Journal of Medicine

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Bactrim™ excels
(trimethoprim and sulfamethoxazole/Roche)

More urinary tract isolates prove sensitive *in vitro*

Percent of isolates of common uropathogens sensitive to BACTRIM and to other antimicrobials

	Escherichia coli	Klebsiella pneumoniae	Proteus mirabilis	Proteus vulgaris	Proteus sp.	Enterobacter sp.	Enterobacter aerogenes	Enterobacter cloacae
BACTRIM TMP/SMX	96% 328,598†	89% 63,551	93% 62,691	84% 4174	91% 4381	88% 1736	96% 7326	92% 11,856
AMPICILLIN	72% 345,209	5% 65,466	85% 67,338	16% 4381	70% 4402	10% 1775	9% 7759	11% 12,091
CEPHALEXIN*	81% 343,339	85% 67,031	92% 67,027	16% 4398	80% 4365	22% 1834	13% 7571	12% 11,846
NITROFURANTOIN	97% 307,785	65% 61,162	7% 59,775	13% 3848	14% 3059	67% 1707	60% 7109	67% 10,830
TETRACYCLINES	76% 322,304	78% 62,627	7% 62,340	31% 4177	4% 4266	69% 1635	86% 7262	79% 11,507

*Analogous to cephalothin, the primary antibiotic disc used in testing.
†Numbers under percentages refer to the projected number of isolates tested.
Source: The Bacteriologic Report, BAC-DATA Medical Information Systems, Inc., Winter Series 1981-82.

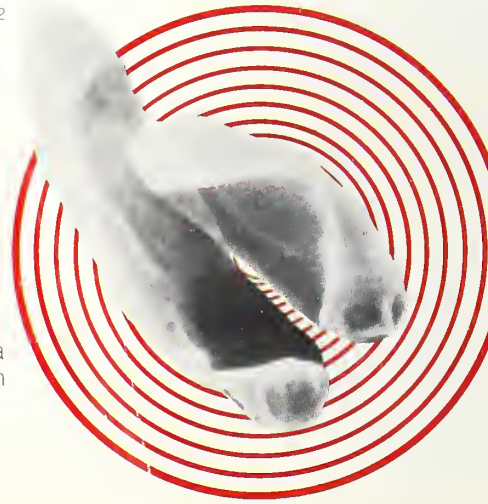
More studies show a lower incidence of bacteriologic recurrence

Patients treated with Bactrim have often remained free of recurrence longer than comparable patients treated with other drugs. In one study, 87 "difficult" patients, 76% of whom were infected with *E. coli*, were treated with Bactrim or cephradine.[1] Although the differences were not statistically significant, the cure rates with Bactrim were 85.4% at two weeks and 72.5% at six weeks, compared to 69.8% and 56%, respectively, with cephradine.

In a study of 93 women treated with either Bactrim or cephalexin for *E. coli* or *Proteus mirabilis* infections,[2] the cure rate six weeks after the course of treatment remained significantly higher with Bactrim than with cephalexin (84.6% vs. 58.5%).

Bactrim is indicated for the treatment of recurrent urinary tract infections due to susceptible strains of *Escherichia coli*, *Klebsiella-Enterobacter* and the *Proteus* species. However, it is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single antimicrobial agent rather than the combination.

Scanning electron micrograph showing 24-hour effect of Bactrim at 5 × MIC on *E. coli in vitro*. Viability studies indicated that such distorted bacteria were killed.[6]



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CORGARD®
(nadolol tablets)
ONCE A DAY FOR HYPERTENSION

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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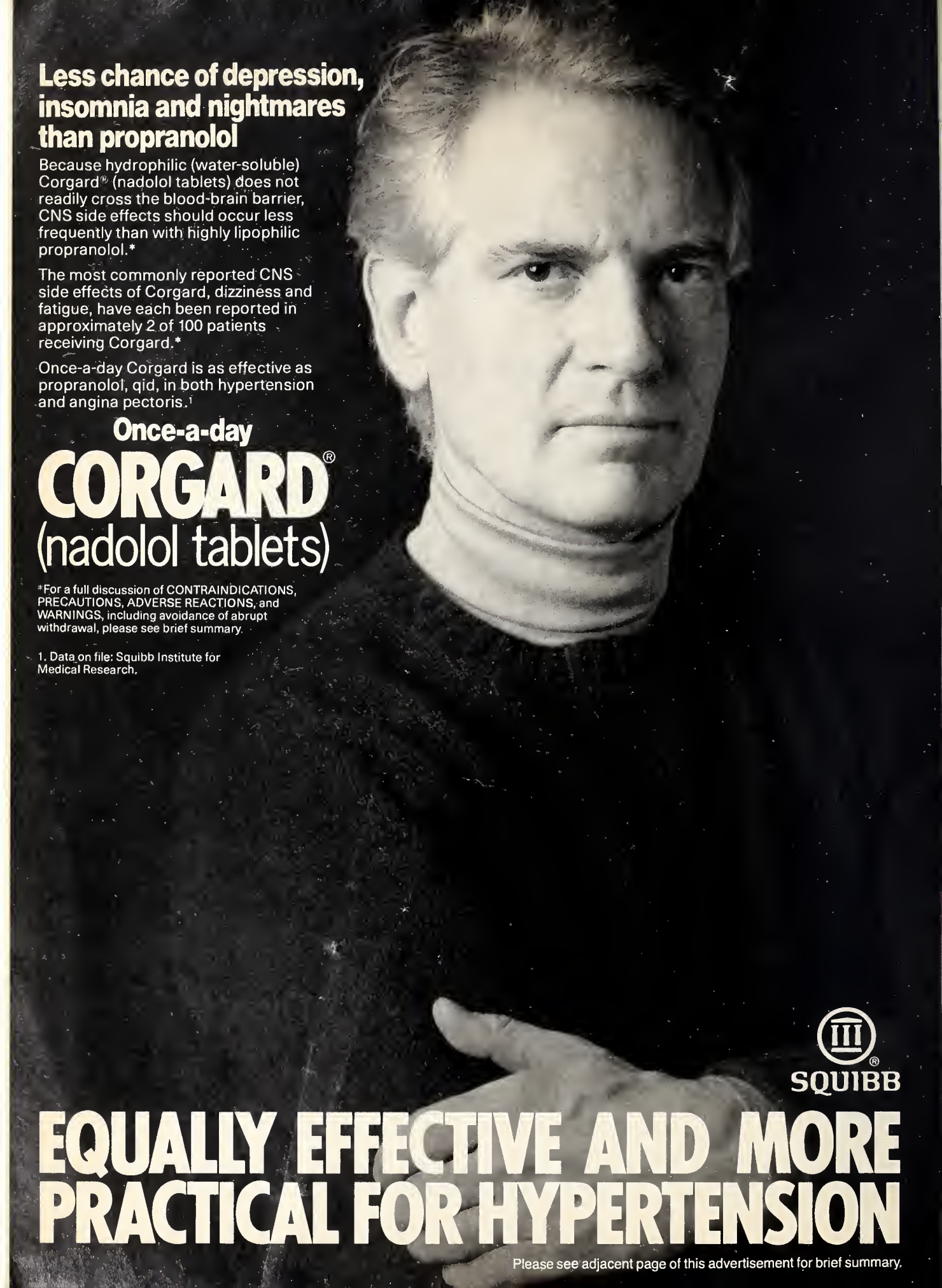

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Once-a-day Corgard is as effective as propranolol, qid, in both hypertension and angina pectoris.[1]

Once-a-day

CORGARD®
(nadolol tablets)

*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.

1. Data on file: Squibb Institute for Medical Research.

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WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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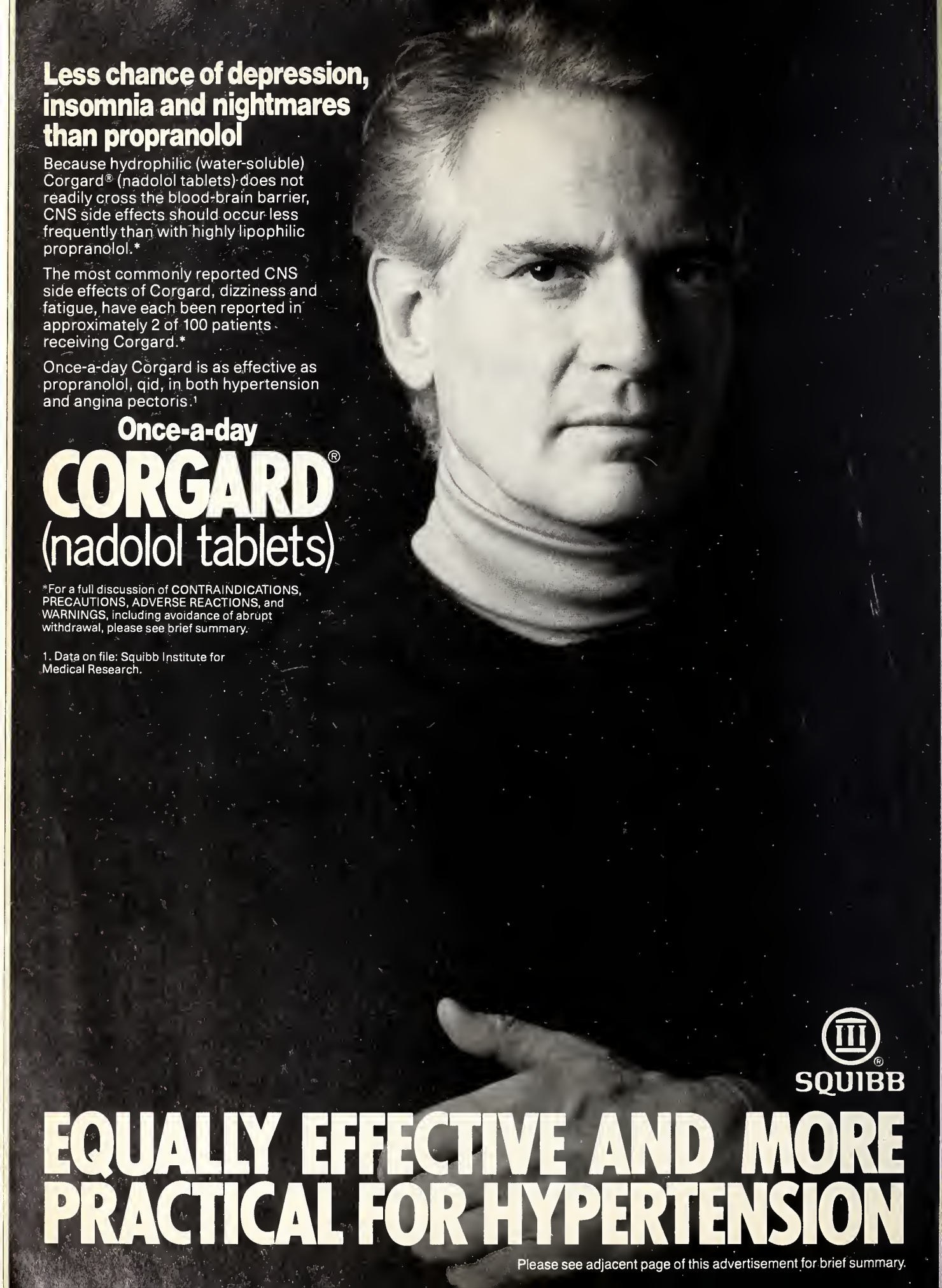
★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.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Once-a-day
CORGARD®
(nadolol tablets)
*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.
1. Data on file: Squibb Institute for Medical Research.
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Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

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WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

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Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

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Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

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OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

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Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

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Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

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For full prescribing information, consult package insert.

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Dr Kettel is Dean of the University of Arizona, College of Medicine, Tucson.

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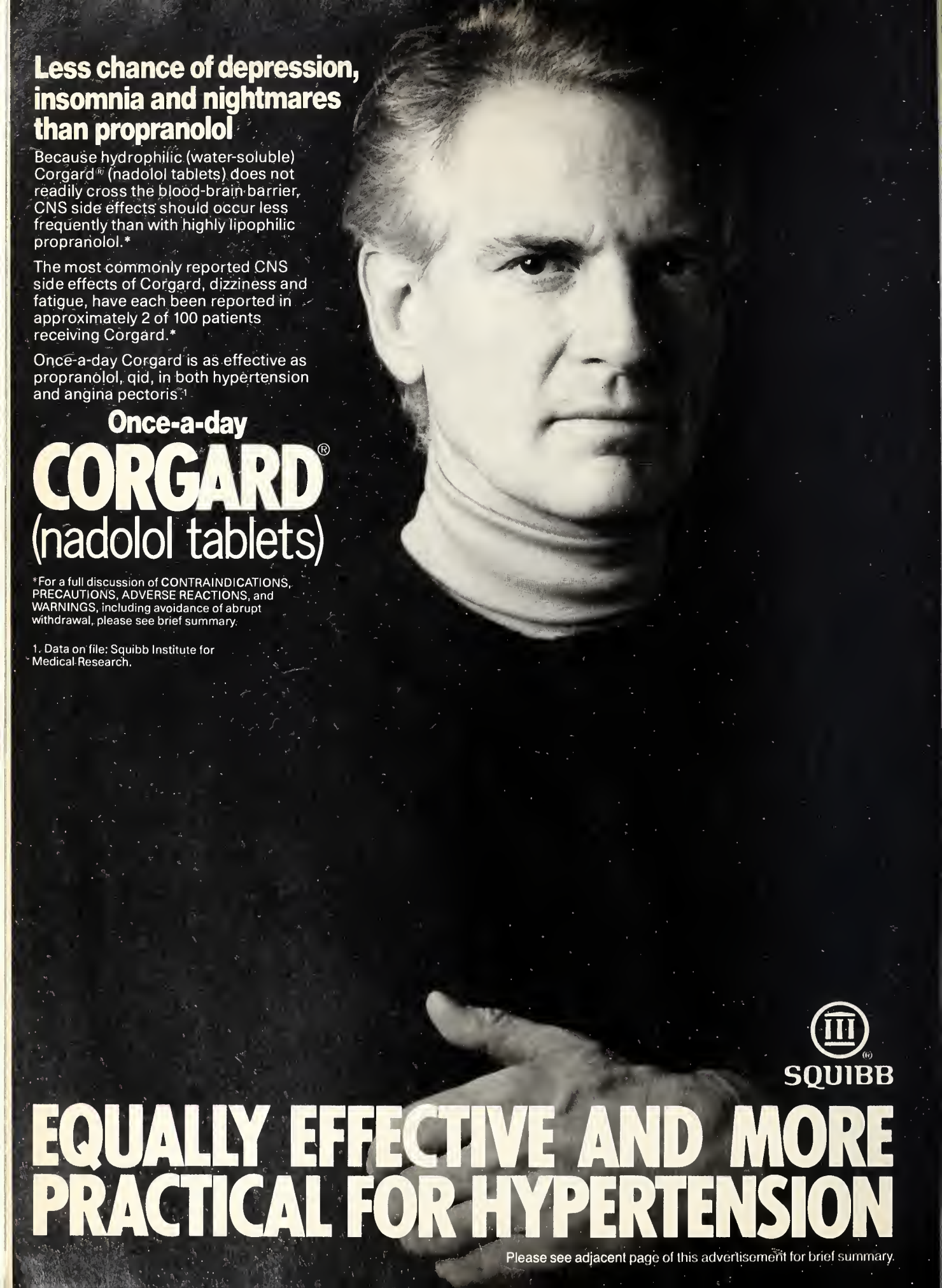
★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.


Less chance of depression, insomnia and nightmares than propranolol
Because hydrophilic (water-soluble) Corgard® (nadolol tablets) does not readily cross the blood-brain barrier, CNS side effects should occur less frequently than with highly lipophilic propranolol.*
The most commonly reported CNS side effects of Corgard, dizziness and fatigue, have each been reported in approximately 2 of 100 patients receiving Corgard.*
Once-a-day Corgard is as effective as propranolol, qid, in both hypertension and angina pectoris.[1]
Once-a-day
CORGARD®
(nadolol tablets)
*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.
1. Data on file: Squibb Institute for Medical Research.
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Please see adjacent page of this advertisement for brief summary.

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CORGARD®
(nadolol tablets)
ONCE A DAY FOR HYPERTENSION

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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Issued: July 1983

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Dr Epstein is Professor and Vice Chairman, Department of Psychiatry, and Associate Director, Langley Porter Psychiatric Institute, University of California, San Francisco.

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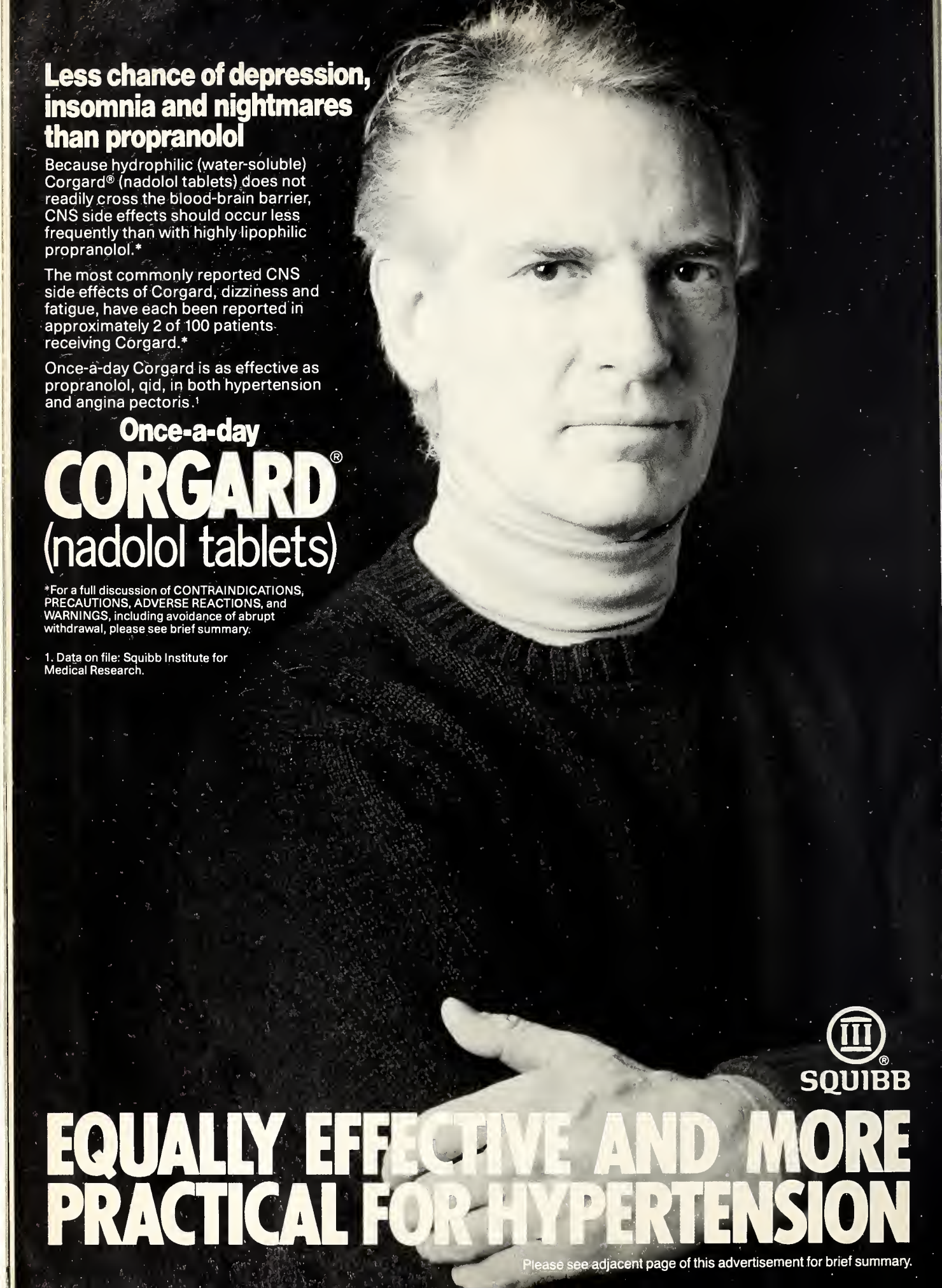
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Dr Terr is Clinical Professor of Medicine and Director, Allergy Clinic, Stanford University School of Medicine, Stanford, California.

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Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

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OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

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Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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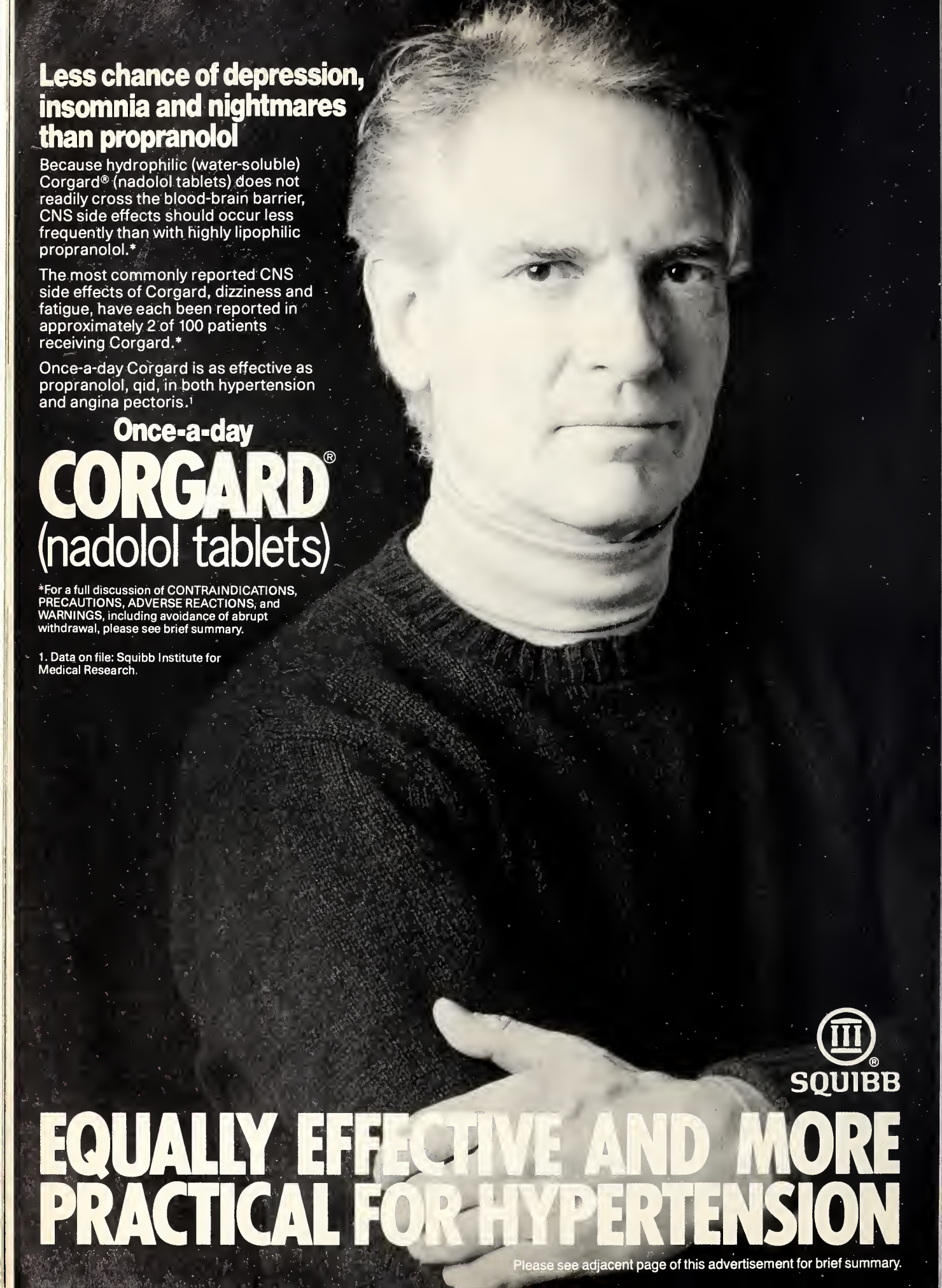
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*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.
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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

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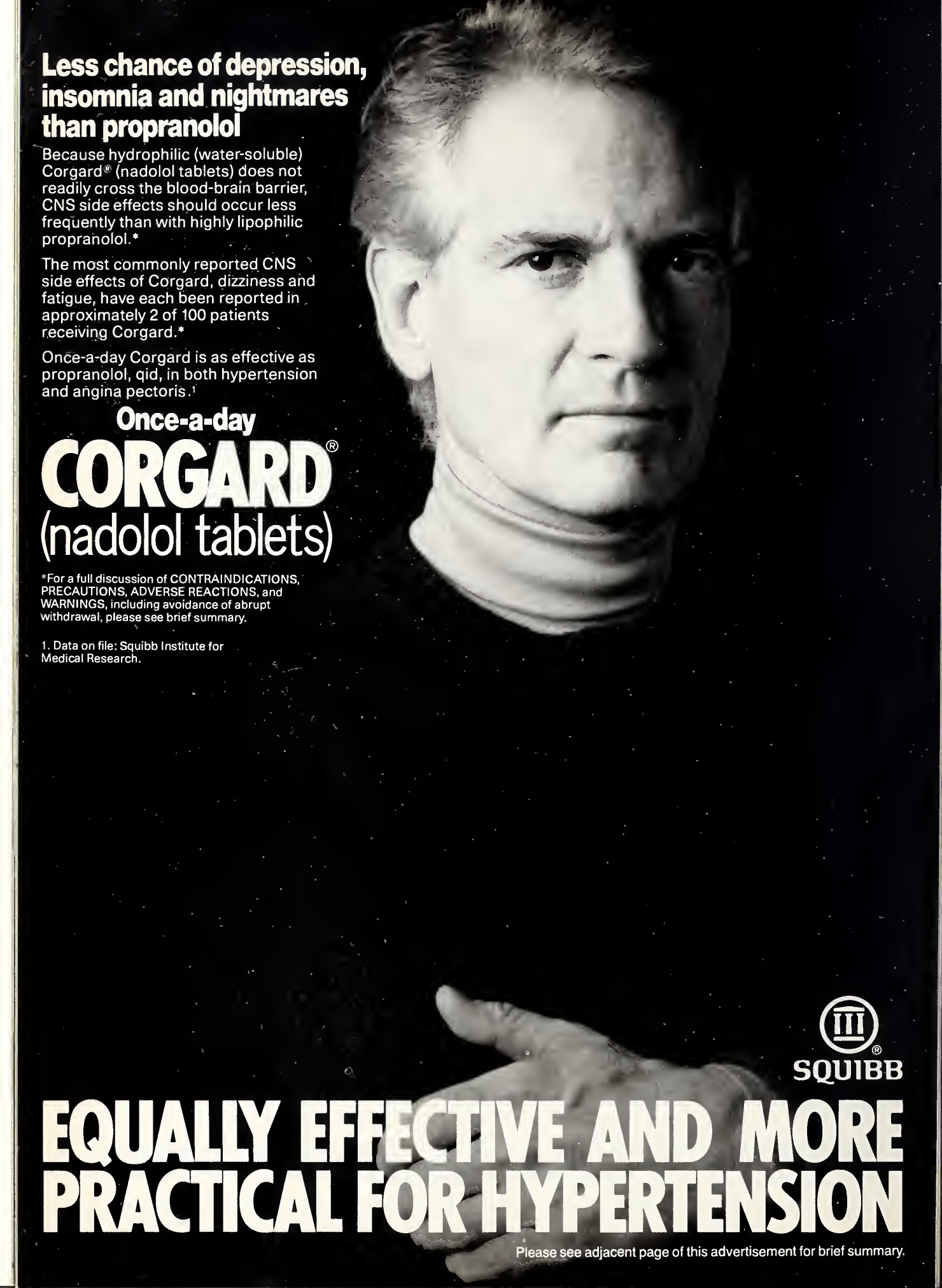
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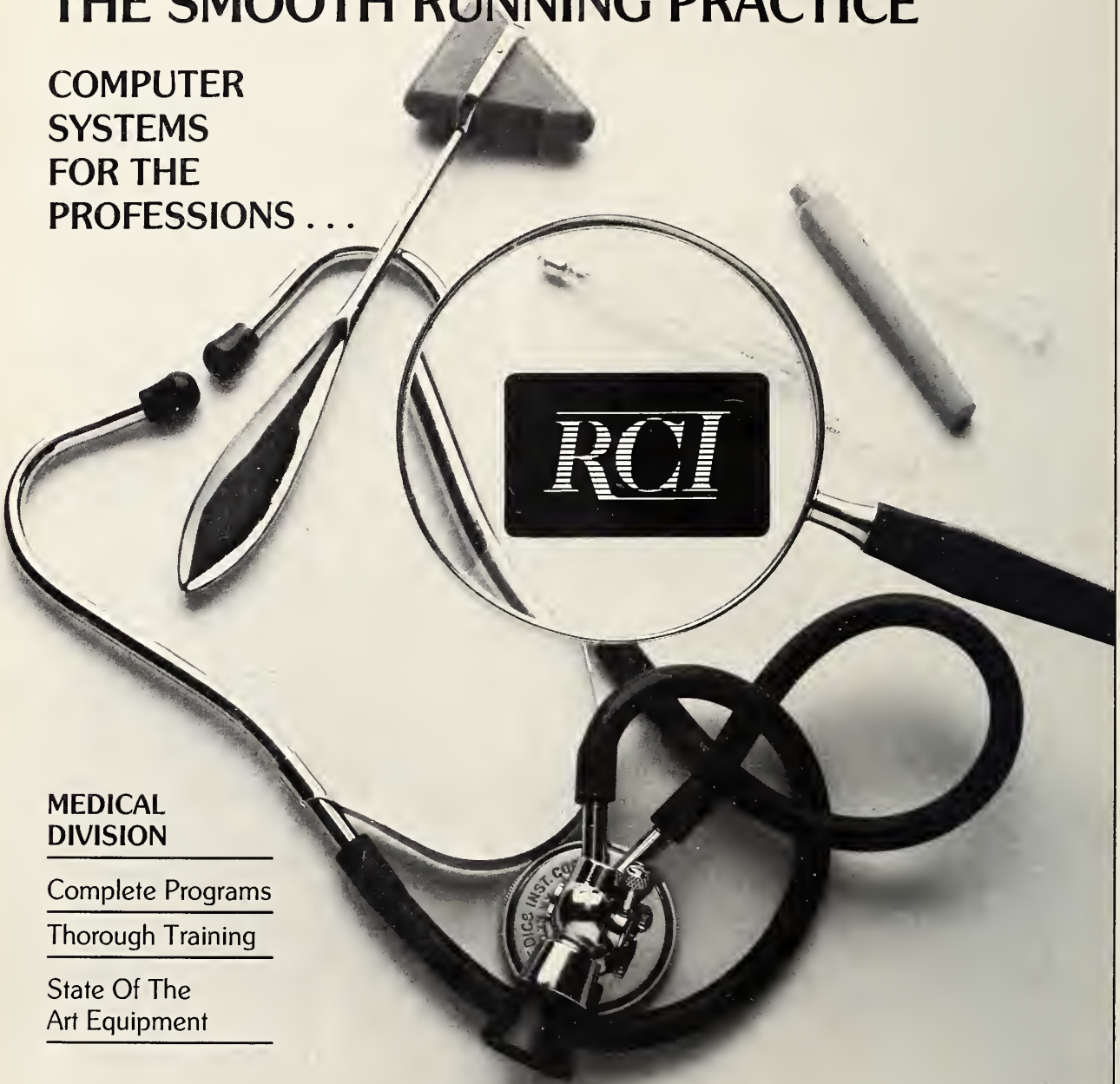

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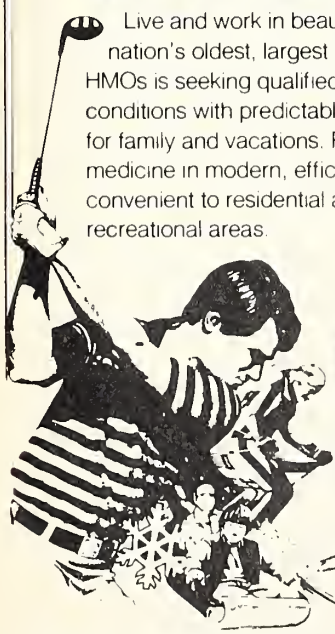

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A New Section, An Old Hope

This issue of The Western Journal of Medicine inaugurates a new section and responds to an old hope. The Clinical Investigation Section has been brought to life through an agreement reached between the *WJM* and the five scientific societies that meet in Carmel each February. These societies—the Western Society for Clinical Investigation, the Western Association of Physicians, the Western Society for Pediatric Research, the American Federation for Clinical Research (Western Section) and the Society for Investigative Dermatology (Western Region)—exist almost exclusively to foster biomedical research, nurture promising young investigators and encourage collegiality among medical school faculty in the western United States and western Canada.

The Carmel meetings are enormously successful, but something always seems to be missing the rest of the year. Consequently, the Western Research Societies have periodically hoped to start a new research journal. However, fiscally difficult times and the obvious surfeit of scientific publications argued against such a venture. At the same time, the *WJM* has never been completely satisfied with the quality and quantity of articles it has published dealing with clinical investigation in its formal sense—that is, prospective studies of humans or human tissues designed to provide insights into pathogenesis and treatment of disease states. Happily, these bilateral, gnawing concerns have been transformed by the journal and the societies into the jointly sponsored enterprise that follows.

The new Clinical Investigation Section welcomes submission of manuscripts reporting top-quality, imaginative research into the full gamut of human pathophysiology—medical, surgical and pediatric. At first, the section probably will not appear with every issue unless we are immediately flooded with superb manuscripts—a delightful but unlikely prospect. However, within a year we hope this section will be a regular part of each issue. As Editor of the section, I will rely heavily on the support and advice of the scientific advisory board, which is composed of representatives from each of the 20 medical schools in the western United States and western Canada. Since the success of this new section is clearly dependent upon your support and participation, we hope you will be as excited and enthusiastic as we are about grasping this opportunity to round out the excellence of the *WJM* and to promote an even healthier interaction among clinical investigators in the West.

R. Paul Robertson, MD
Editor for Clinical Investigation

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Clinical Investigation

Treatment of Advanced Malignancy With Plasma Perfused Over Staphylococcal Protein A

F. ROY MacKINTOSH, MD, PhD; KIM BENNETT, MS; STEVEN SCHIFF, MD; JOHN SHIELDS, MD, *and* STEPHEN W. HALL, MD, *Reno, Nevada*

A total of 14 extensively pretreated patients with advanced and progressive malignancy were given 140 infusions of autologous plasma that had been perfused over staphylococcal protein A bound to an agarose gel (Sepharose). Infusions ranged in volume from 35 ml to 260 ml (mean, 70 ml), and the quantity of protein A used ranged from 1 to 30 mg per 100 ml of plasma (mean, 10 mg). Acute toxic reactions included fever (21%), chills (18%), nausea (17%), vomiting (8%), pain (9%) and bronchospasm (2%). Four patients did not have an acute toxic reaction and no chronic or cumulative toxic effects were identified. In two patients there was objective tumor regression and in five there was stabilization of disease lasting from 4 to 12 weeks. Further study of this treatment modality is warranted.

There has been considerable interest in the role of serum "blocking factors" in the pathogenesis of malignancy.[1-4] The finding that these factors are immune complexes or immunoglobulins led to the concept that their removal by nonspecific[5] or specific[6,7] means might prove useful in the treatment of malignancy. The observation that staphylococcal protein A nonspecifically binds IgG and its complexes via the Fc receptor[8] led to its use as an "immunoadsorbent" in the treatment of various malignant diseases of cats,[6] dogs[7,9,10] and humans.[11-15] Terman and co-workers[15] noted that small volumes of protein A-treated autologous plasma produced tumor regression in humans with significant but manageable acute toxic effects, which observation led us to undertake an evaluation of this novel treatment modality. We report our initial phase I experience in treating advanced malignancy with autologous plasma perfused over staphylococcal protein A covalently bound to an agarose gel (Sepharose).

Patients, Materials and Methods

Patients with biopsy-proved malignancy who had progressive cancer following standard therapy (including at least one course of chemotherapy) and for whom no established therapy nor any potential cure could be offered were eligible for this study. Informed consent for participation was obtained according to institutional policies.

Patients received no other therapy during the study and had received no therapy for at least four weeks before study entry, except for radiotherapy to locally symptomatic or threatening disease sites. These irradiated sites were not considered in assessing response to plasma therapy.

Autologous plasma was obtained by phlebotomy using standard blood donor sets (450-ml capacity, with citrate-dextrose-adenosine anticoagulant) and plasma transfer packs. Red blood cells were reinfused on the day of phlebotomy. Plasma was treated by centrifugation at 3,000 G for 30 minutes, followed by passage over a column of Sepharose-bound protein A (Pharmacia, Inc, Piscataway, NJ). The quantity of protein A varied from 1.0 to 30 mg per 100 ml of plasma. Treated plasma was filtered through a 0.22-micron filter, packaged in standard blood product administration sets and either administered fresh or stored frozen

Refer to: MacKintosh FR, Bennett K, Schiff S, et al: Treatment of advanced malignancy with plasma perfused over staphylococcal protein A (Clinical Investigation). West J Med 1983 Jul; 139:36-40.

From the Department of Medicine, University of Nevada School of Medicine, Reno.

Supported in part by a grant from the Reno Cancer Center.

Submitted, revised, December 17, 1982.

Reprint requests to F. Roy MacKintosh, MD, PhD, Department of Medicine, Division of Oncology, Veterans Administration Medical Center, 1000 Locust Street, Reno, NV 89520.

at −70°C until use. From one to four (median three) separate packages of treated plasma were prepared from each unit of blood. For patients on stable doses (see below), equal aliquots of plasma were packaged, whereas for patients still undergoing dose escalation, a typical preparation would be packaged in volumes of 50, 100 and 150 ml. Plasma processing was done in a laminar flow hood at ambient temperature, and sterility was tested on aliquots of treated plasma using standard blood culture media. No growth was observed in any cultures.

In the absence of detailed information about the mechanism of action of this therapy, the definition of "dose" is problematic. We assumed that the potential toxic or antitumor activity of the treated plasma was directly related to the volume of plasma and to the ratio of protein A to plasma used in the preparation of the treated plasma. Based on the report by Terman and associates,[15] we chose 50 ml of autologous plasma treated at a ratio of 1.0 mg of protein A per 100 ml as a starting dose. For the ninth and subsequent patients, the planned starting dose was 50 ml of plasma treated at 4.0 to 5.0 mg of protein A per 100 ml of plasma. After each infusion without a significant toxic reaction, dosage was escalated by 50% to 100% for the next treatment. We considered the dose at each treatment to be the product of treated plasma volume (ml) × (mg of protein A per 100 ml of plasma), and dose escalation consisted of increasing either the volume of plasma or the amount of protein A used in its preparation.

The study plan was to infuse treated plasma twice a week, increasing the dose at each treatment until an easily measured acute toxic effect was observed, and then to continue at this maximally tolerated dosage for a total of two months or until disease progression. For patients living at a considerable distance for whom twice-a-week visits were not possible, the treatment schedule was modified to include three infusions of treated plasma on days 1, 3 and 5, and to repeat the cycle (with dose escalation as indicated) on day 15.

Treated plasma was infused over 5 to 15 minutes. Vital signs were monitored at intervals of 15 to 30 minutes and subjective reports of a toxic reaction recorded for two hours thereafter or until stable. Fever and chills were treated by giving acetaminophen and diphenhydramine hydrochloride and for patients receiving a stable (nonescalating) dosage, these medications were used prophylactically if warranted by previous symptomatic toxic reactions.

Patients were evaluable for toxic reactions after one infusion and for response after four infusions of treated

TABLE 1.—*Clinical Characteristics of Patients Studied*

Patient	*Diagnosis*	*Age/Sex*	*Weight (kg)*	*Karnofsky Status*	*Disease Sites**	*Prior Therapy†*	*Schedule Planned‡*
1	Adenocarcinoma, lung	30 ♂	50	20	L	Chemotherapy (3)	I
2	Adenocarcinoma, breast	44 ♀	48	40	HO	Chemotherapy (3), radiation, surgical	I
3A§	Adenocarcinoma, breast	43 ♀	200+	40	LO	Chemotherapy (3), radiation, surgical	I
3B§	Adenocarcinoma, breast	43 ♀	200+	40	LO	Chemotherapy (3), radiation, surgical	I
4	Squamous carcinoma, lung	77 ♂	78	40	LP	Chemotherapy (1)	II
5	Squamous carcinoma, lung	53 ♂	52	70	DO	Chemotherapy (1), radiation, surgical	I
6	Squamous carcinoma, lung	54 ♂	66	80	L	Chemotherapy (1), radiation, surgical	II
7	Squamous carcinoma, head and neck	65 ♂	61	80	DN	Chemotherapy (1), radiation, surgical	II
8	Paraganglioma	53 ♀	45	50	LOP	Chemotherapy (1), radiation, surgical	I
9	Squamous carcinoma, lung	66 ♂	82	60	LO	Chemotherapy (1), radiation, surgical	II
10	Renal carcinoma	44 ♂	54	40	DLO	Chemotherapy (2), radiation, surgical	I
11	Melanoma	55 ♂	68	50	N	Chemotherapy (3), radiation, surgical	I
12	Adenocarcinoma, colon	54 ♀	50	40	HL	Chemotherapy (1), radiation, surgical	I
13	Adenocarcinoma, colon	35 ♀	98	70	H	Chemotherapy (1), radiation, surgical	I
14	Adenocarcinoma, breast	70 ♀	47	50	P	Chemotherapy (2), surgical	I

*Disease sites are: D=skin, H=liver, L=lung, N=nodes, O=osseous, P=pleura.
†Numbers in parentheses indicate the number of chemotherapy regimens previously used.
‡Schedule I consists of twice-a-week infusions. Schedule II consists of three infusions every other week.
§Patient 3 had two courses of therapy separated by five weeks.

TABLE 2.—*Acute Toxic Effects of Plasma Perfused Over Protein A Agarose Gel (Sepharose)*

Dosage Range (ml×mg protein A/100 ml)	*Doses Number*	*Fever**	*Rigor*	*Nausea*	*Broncho-spasm*	*Local Pain*	*Hypo-tension*
		Number of Patients					
35- 100	17	6	6	6	..	..	..
101- 200	22	4	3	1	..	..	..
201- 300	16	1	1	1	..	1	..
301- 500	30	5	4	8	..	5	1
501-1,000	18	6	5	5	2	4	..
1,001-1,500	17	3	2	2	1	2	..
1,501-2,500	8	3	3	..	..	..	..
2,501-3,500	2	1	1	1	..	..	..

*Fever is defined here as elevation of oral temperature exceeding 37.8°C.

plasma. One patient (case 7) was nonevaluable because of lack of measurable disease.

Results

Of the initial 14 patients, all are evaluable for toxic reactions and 12 are evaluable for response. The nonevaluable patients include one who died early and one who had no evaluable disease. The initial clinical characteristics of these patients are shown in Table 1. The volumes of plasma for individual infusions ranged from 35 ml to 260 ml (mean, 70 ml), and the ratios of protein A per 100 ml of plasma ranged from 1.0 to 30 (mean, 10). Dosage ranged from 35 to 3,000 arbitrary units. Significant toxic effect was seen at doses as low as 100 units, but some patients had no toxic reaction at the highest level attained. All toxic reactions except hypercalcemia were evident within an hour. There was no evidence that toxicity was cumulative or schedule dependent for the two schedules used. Freshly prepared plasma and stored frozen plasma were equitoxic. About 80% of treatments were given with previously frozen treated plasma. Table 2 summarizes the observed toxic effects as a function of dosage. The most common toxic reactions were fever and chills. These were generally not associated with life-threatening changes in blood pressure or respiratory state, though patients 4 and 14 (Table 1) had a total of three episodes of bronchospasm. Subcutaneous administration of epinephrine was required for relief in one case. In most cases, chills were noted within about 30 minutes of beginning the infusion, and maximal temperature was reached in 30 to 90 minutes. In only one patient did a treatment-associated fever persist for more than two hours.

Other toxic reactions included a single episode of hypotension, which required no specific therapy and resolved within ten minutes. Three patients had nausea following therapy (cases 6, 8 and 14, Table 1). There were two episodes of treatment-related diarrhea. Only one patient (case 8) had exacerbations of local pain at tumor sites with therapy.

In one patient with breast cancer and extensive bone metastasis, hypercalcemia developed on two occasions 72 to 96 hours after an infusion of treated plasma (Figure 1). In both instances, control of the serum calcium level required admission to hospital for infusions of saline and mithramycin. Table 3 gives a summary of the course of each patient, including data on doses of treated plasma, fever, duration of therapy and clinical response.

As this was a phase I study, its objective was to determine toxicity of treatment. Significant antitumor effects were observed in 2 of 12 evaluable patients, however, and an additional five patients had stabilization of disease for four to eight weeks. The other five patients had definite or probable progression of tumor within the first four weeks of treatment. One patient with progressive disease and renal carcinoma (case 7) received dexamethasone for spinal cord compression during therapy with protein A-treated plasma, and this may have interfered with toxic effects or therapeutic response (or both). Two patients (cases 2 and 3) for technical reasons received rather low doses of plasma, and the latter had a toxic reaction only once at the highest dosage used, after which she refused further therapy. Only one patient (case 6) had both fever and chills with treatment and prompt progression of tumor.

A brief description of responses in two patients will show the quality of tumor regression seen.

Patient 4 was a 77-year-old man with squamous

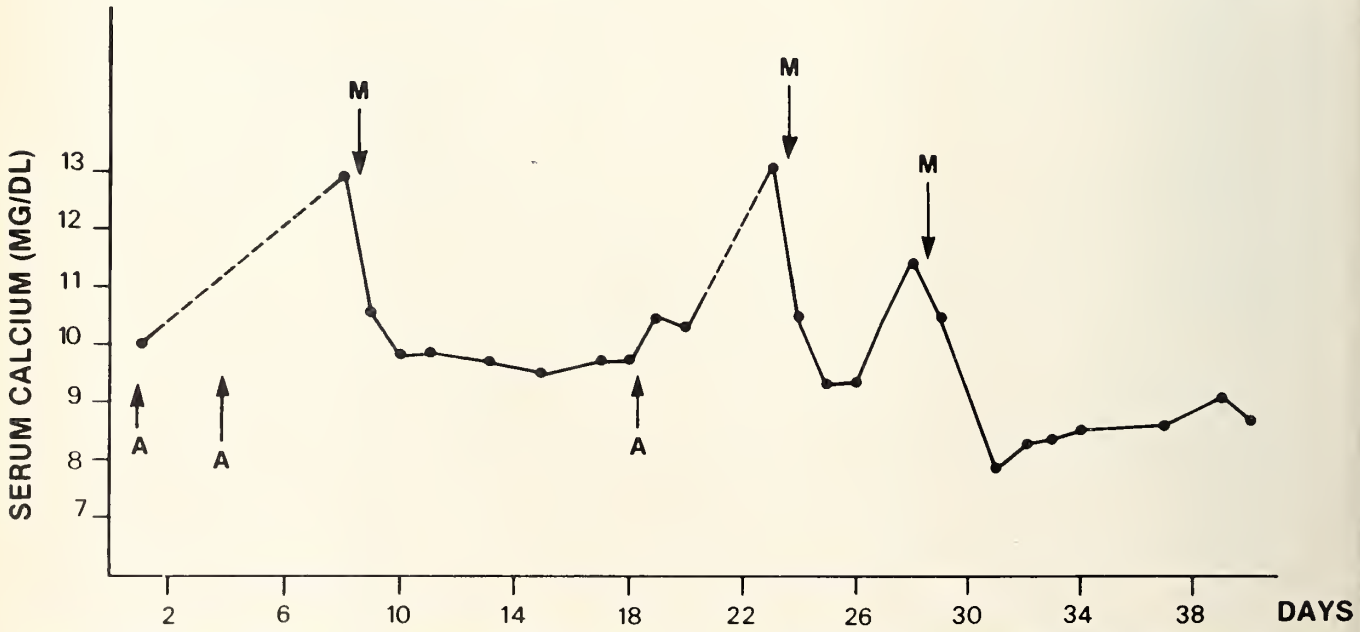

Figure 1.—Serial measurements of serum calcium in patient 2 are shown. Arrows indicate times of administration of treated plasma **(A)** or mithramycin **(M)**.

carcinoma of the lung. Figure 2 shows a series of x-ray films taken over the first six weeks of his therapy. His pleural effusion resolved and collapsed segments of lung reexpanded. During therapy a central abscess developed in a large right upper lobe mass, which was the site of his primary tumor. Ultimately, an associated pneumonia led to his death after 65 days of plasma therapy.

Patient 8, a 54-year-old woman with paraganglioma, had a left retroorbital mass, multiple pulmonary nodules, bone metastasis with pathologic fractures and bilateral pleural effusions. During plasma therapy, there was reduction of proptosis and recovery of the ability to read and embroider, which had been impossible because of diplopia and blurring of vision. Pleural effusions resolved, new bone formation was noted in an area of pathologic fracture and multiple pulmonary nodules remained stable for 12 weeks.

Discussion

In any phase I study, the central goal is to define toxic effects and to establish suitable dose-schedule relationships that will allow subsequent studies to delineate the spectrum of antitumor activity of a new therapy. The uncertainty about the mechanism of action of this therapy, however, makes the definition of dose problematic. We defined arbitrary "units" of dosage based on the assumption that effects would be related to volume of plasma infused and quantity of protein A used. Starting doses were based on the limited literature available regarding dosage[12,15] and were escalated progressively. Despite this dose escalation,

TABLE 3.—*Treatment Data for Patients Studied*

Patient	*Number of Treatments*	*Duration of Therapy (Days)*	*Initial Dose (units)*	*Initial Amt Protein A (mg/100 ml plasma)*	*Maximum Dose (units)*	*Maximum Amt Protein A (mg/100 ml plasma)*	*Maximum Temperature (°C)*	*Clinical Response*
1	2	3	60	2.0	120	2.0	37.4	NE
2	3	26	35	2.5	85	2.5	37.7	PD
3A	8	26	85	2.0	400	8.0	37.5	S
3B	1	1	..	..	800	8.0	37.9	NE
4	12	65	200	5.0	720	16.0	39.7	PR
5	8	30	100	6.2	200	6.2	39.1	PD
6	15	60	100	5.0	2,400	50.0	38.7	S
7	10	31	120	6.1	750	16.0	38.6	NE
8	27	84	100	5.0	1,100	40.0	37.2	MR
9	10	42	250	12.5	3,000	90.0	38.5	S
10	6	12	200	12.0	1,050	12.0	37.4	PD
11	5	14	660	20.0	1,250	29.0	36.9	PD
12	5	9	250	12.0	1,000	34.0	38.3	PD
13	14	42	200	11.0	2,000	60.0	38.6	S
14	14	60	250	12.0	1,500	35.0	38.7	S

NE=not evaluable; PD=progressive disease; S=stable; PR=partial regression of more than 50%; MR=minor response.

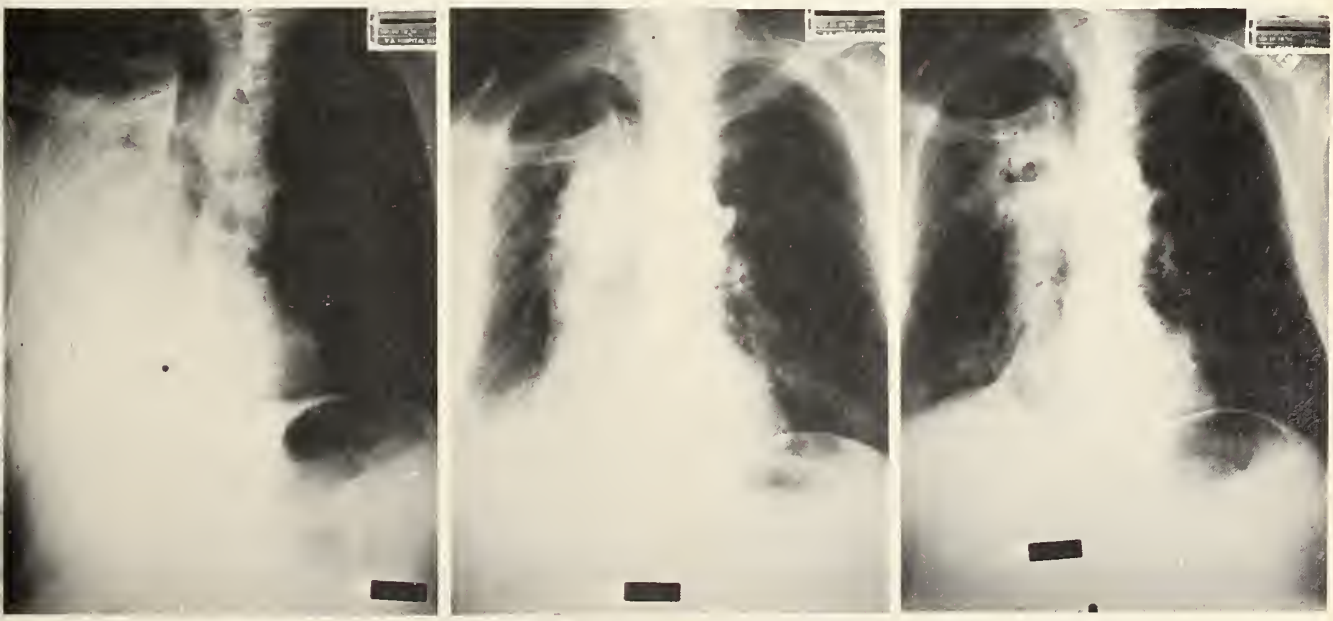

Figure 2.—Left, Chest radiograph of patient 4 at the start of plasma therapy. **Center,** After four weeks of therapy, pleural effusion has decreased, showing collapsed segments of lung. **Right,** After six weeks of therapy, some collapsed portions of lungs have reexpanded and the primary tumor shows an air-fluid level.

four patients had no observable or subjective toxic reactions. The toxic effects described were generally acute, well tolerated and easily managed. This treatment regimen is suitable for phase II trials in refractory malignant conditions. Based on our initial experience, we recommend beginning therapy with plasma treated with Sepharose-protein A at a ratio of 4 mg of protein A per 100 ml of plasma. An initial infusion of 50 ml of treated plasma can be followed at one- to three-day intervals by volumes of 100 ml and 150 ml from the initial phlebotomy. If no toxic reaction is encountered, protein A ratios can be successively doubled for subsequent phlebotomies and similar volume escalations used at each protein A-to-plasma ratio. Because of the wide range of doses associated with toxic reactions in our patients, we think that individual patients may have pronounced differences in their maximal tolerated doses. Because of the possibility of a relationship of response and toxic reaction, low starting doses with rapid escalation may be necessary in phase II or III studies of this treatment modality.

Understanding the mechanism of action of the therapy will enhance our ability to define dosage and to select appropriate patients for therapy based on in vivo or in vitro predictive tests. The observation of antitumor effects after infusion with small volumes of treated plasma[15] or after infusion of larger volumes treated inadequately to produce complete immunoadsorption[11,13,14] suggests that the removal of "blocking factors" is unlikely to explain the effects observed. When Holohan and colleagues[7] measured blocking activity in dogs with breast cancer before and after protein A-treated plasma infusions, they concluded that "complete removal of blockers is neither necessary nor sufficient" for tumoricidal effects. Terman and co-workers[15] found immunoglobulins and complement on the surface of tumor cells in biopsy specimens taken after treated plasma infusions. If this finding can be confirmed and correlated with response, it could provide the basis for an in vivo "predictive" test for efficacy in patients who have lesions in which a biopsy is easily done, giving us useful insight into the mechanism of action of the therapy. Many patients have circulating antitumor antibodies and Clq binds to antibody-protein A complexes.[8] If antitumor antibodies bind to Clq during perfusion of plasma over protein A, these complexes may be competitively removed from protein A by passage of plasma in excess of the protein A-binding capacity and subsequently infused into a patient. Such IgG-Clq complexes could be responsible for initiation of complement activation at the tumor cell surface and thus account for many of the biologic effects observed, including local pain and hyperemia,[15] fever, chills and tumoricidal effects. Other explanations that have been put forth to explain the activity of protein A-treated plasma include an alteration of the balance of opposing immunologic activities[6] or selective adsorption of immune complexes leading to high titers of cytotoxic antibody.[6] Nonspecific leaching of material from the protein A column[16] seems unlikely in view of the wide range of active protein A-containing materials that have been used[6-15] and the chemical stability of the covalent linkages in the preparations we used. The "blocking factor" hypothesis may still be an appropriate explanation for the therapeutic results of plasmapheresis.[11] Of note is that plasmapheresis or plasma exchange does not produce the spectrum of toxic reactions[11] that we and others[15] observed with infusion of small volumes of protein A-treated plasma.

In summary, the distinct biologic effects, including antitumor effects, that we and others[6-15] have observed using protein A-treated plasma suggest that we do indeed have a new therapeutic modality for use in the treatment of cancer. Phase II studies of protein A-treated plasma infusions for a wide range of refractory malignant conditions can be undertaken based on the preliminary evidence of broad efficacy that is developing. Elucidating the mechanism of the antitumor effects produced by this ex vivo perfusion of plasma over protein A should enable us to optimize and standardize plasma treatment and administration. Developing suitable in vitro predictive tests should also be possible and the use of this modality in randomized trials with standard therapies, initially for advanced malignancy and later into treatment programs where there is a curative intent (such as adjuvant chemotherapy for breast cancer), should become possible.

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Separation of Forearm Hemodynamics Into Skin and Muscle Components by Means of *l*-Epinephrine Iontophoresis

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By a combination of iontophoresis of l-epinephrine into the skin of one arm and simultaneous venous occlusion plethysmography in both treated (muscle only) and untreated forearms (muscle plus skin), we examined in 16 normal volunteers forearm blood flow, capillary filtration coefficient and venous capacity at cuff pressure of 40 mm of mercury (VC_{40}) at rest, during tonic finger exercise and after interrupted repetitive finger exercise. Blood pressure did not change during the testing procedure. Forearm muscle conductance was about 60% to 70% of total conductance and was positively correlated with total conductance during rest and exercise. With standard exercises muscle conductance rises to 1½ to 2½ times resting level, and skin conductance rises to 2½ to 4½ times resting level. The capillary filtration coefficient is almost entirely in the muscle. It doubles in value with tonic exercise but decreases to half its resting value after interrupted repetitive exercise despite greatly increased conductance. Therefore, repetitive exercise-induced dissociation between conductance and filtration surface occurs in striated muscle. The mechanism is yet unknown. VC_{40} in muscle is about 84% of total forearm VC_{40}. During tonic exercise muscle VC_{40} was reduced, and during interrupted repetitive exercise the values for muscle and skin returned to resting values. A high correlation between muscle only and muscle-plus-skin for forearm blood flow and the identity between arms for measuring capillary filtration coefficient makes iontophoresis unnecessary for determining these values in forearm striated muscle under these experimental conditions.

Plethysmography using the mercury-in-rubber strain gauge has been used for more than 30 years to measure blood flow to the limbs of animals and humans, but only recently has it been applied to obtain information on vascular filtration coefficient and venous capacity or tone.[1] Vascular filtration coefficient of the limb has been shown to change abruptly during massive intravenous fluid loading,[2] during infusion of acetylcholine under conditions of constant arterial pressure,[3] during tonic and repetitive exercise,[1] during experimental pericardial tamponade in dogs[4] and in association with age and a variety of human diseases known to affect the microcirculation, such as hypertension and diabetes mellitus.[1,5] Because the technique measures events occurring in the vasculature of the skin and muscle, and because the vascular anatomy of these two organs is distinct, it would be useful to be able to separate the plethysmographic curves into skin and muscle components. A potential method for accomplishing this was introduced by Cooper and coworkers,[6] who did *l*-epinephrine iontophoresis in the forearm skin, stopping blood flow in the treated skin as far down as the dermal fat pad. Cooper showed in a coauthor that skin blood flow is reduced to zero by this

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technique, as determined by gross examination of the skin on heating and by noting the absence of bleeding from skin incisions. This effect lasts from 90 minutes to two hours during which time measurements can be made in both arms simultaneously—vascular changes occurring in the treated arm only in muscle, and in the untreated arm in both skin and muscle. By suitable subtraction techniques, it should be possible to separate skin and muscle plethysmographic variables, including forearm vascular conductance, capillary filtration coefficient and venous capacity at an arbitrary cuff pressure to occlude the upper arm veins. Zelis and colleagues have used this technique to measure conductance only.[7] We found that although 32% to 47% of the conductance and 19% to 32% of the venous capacity of the forearm is in skin, nearly all capillary filtration occurs in muscle. Moreover, the previously reported dissociation phenomenon[1,5] of exercise-induced increase in conductance with reduced capillary filtration coefficient is a property of the circulation of striated muscle.

Materials and Methods

This study was conducted using paid, healthy, informed volunteers. They signed consent forms approved by the Human Subjects Committee at the University of Arizona Health Sciences Center. The data are from a population of 16 persons with a mean age of 27.9 years ±0.8 standard error of the mean, a mean weight of 64.6±3.5 kg and a mean blood pressure of (118±2)/(79±2) mm of mercury. To compute mean blood pressure, we added a third of the pulse pressure to the diastolic measurement, which resulted in an overall mean blood pressure of 87±2 mm of mercury. There were 14 women and 2 men. The plethysmographic curves in the men did not skew the results in either direction. Subjects arrived at either 9 or 11 AM to a quiet and comfortable laboratory that had an ambient temperature of 28°C; they were then instructed to wash the dominant arm and the ipsilateral leg with Ivory soap. The skin of the forearm from elbow to wrist and the leg from knee to ankle was then defatted with acetone and air dried. The skin was carefully searched for any occult breaks and these areas were avoided when a technician wrapped electrodes around the arm and leg. In an earlier pilot study in a volunteer who had shaved her legs before the study, the iontophoretic procedure caused three punctate electrochemical burns over the lower leg. We subsequently told the female volunteers not to shave their legs within 24 hours of the test and there have been no further burns.

Powdered *l*-epinephrine was dissolved in 6N hydrochloric acid solution. The concentrated salt was then diluted in a beaker covered with aluminum foil and filled with sterile water, resulting in a final concentration of 1/2,000 or 0.5 grams per liter. Wide gauze rolls were soaked in the solution and loosely wrapped in two layers around a subject's arm. The soaking bandage was then wrapped with a multiperforated coil of intravenous tubing to allow introduction of fresh solution during the procedure. Aluminum foil was used as the

Figure 1.—Results of 20 mA of current applied to right arm through a solution of 1/2,000 *l*-epinephrine for 20 minutes. Note the sharply demarcated ischemic zone.

endplate of the electrode, and the foil was held in place with a disposable elastic bandage. A similar electrode was made for the ipsilateral leg but the solution was made of 0.9% sodium chloride in sterile water. An electrical source specifically designed and built for this project* was connected to the subject with the anode on the arm and the cathode on the leg. The seat of electromotive force was a nickel-cadmium rechargeable battery capable of delivering up to 24 volts at 0 hertz. Current was read by an operator and the subject from the front of the source and was slowly dialed from 0 to 20 mA as the person's comfort dictated. Because the act of changing the current is itself associated with opening of new electrical pathways and hence new pain fiber stimulation, it was necessary to make frequent stops on the way up to 20 mA. The person was encouraged to report any "hot spots." When these occurred, the extant current was held constant while fresh solution was applied to the arm or the leg. Hot spots occurred most frequently on the leg, probably because of the cathodal reduction of $H+$ to gaseous hydrogen with the formation of sodium hydroxide in concentrations that changed the leg fluid pH from 5.0 at the start to 9.0 at the end of the procedure. In most cases, fresh flushing of the bandages was all that was required to eliminate each hot spot. If this was ineffective, the current was slowly dialed to zero and the affected limb unwrapped and inspected. Occasionally a break or a nevus marked the hot spot, which would be avoided in the next wrapping. In a rare instance the study was terminated if we could not avoid the hot spot.

After 20 mA of current was established (usually requiring 13 to 14 V), we waited 20 minutes before slowly dialing the current to zero. The subject usually read or slept during this time. After 20 minutes, the electrode and bandages were removed and the skin dried. The effect was always dramatic (see Figure 1),

*Dr Emanuel Furst and the Division of Biomedical Engineering, University of Arizona College of Medicine, constructed the iontophoresis device.

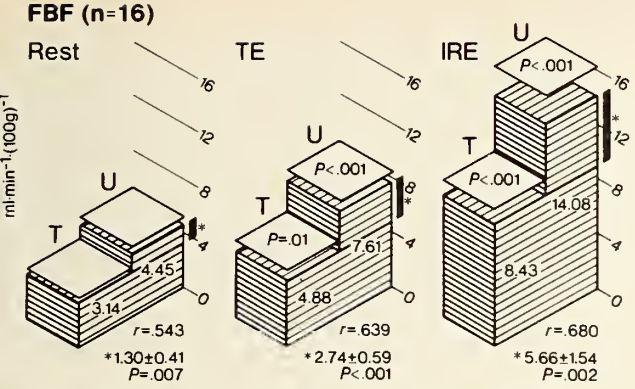

Figure 2.—Results of forearm blood flow (FBF) with epinephrine iontophoresis, in the treated arms (T) compared with the untreated arms (U) at rest, during tonic exercise (TE) and after interrupted repetitive exercise (IRE). The heights of the columns represent values for the treated and untreated arms; the plates represent one standard error of the mean; the solid bars with values given after asterisk represent the values and significance of differences between T and U; the *P* values on the plates represent the significance of the difference from control, and the *r* values are the Pearson correlation coefficients between T and U.

resulting in a sharply demarcated ischemic area where the arm electrode had been.

Routine venous occlusion plethysmography was then carried out in both arms by techniques reported elsewhere.[1,8] The resting period was repeated twice, followed by two periods of tonic forearm exercise during which the subject grasped two self-locked blood pressure cuffs to one-third maximal capacity. The final period followed a five-minute rest and was called the interrupted repetitive exercise, which consisted of a venous occlusion run immediately following 90 seconds of opening and closing the fingers tightly around a self-locked blood pressure cuff.

The plethysmographic curve was recorded during an abrupt increasing of pressure in a cuff around the upper arm to 40 mm of mercury. Blood pressure was determined by auscultation between each run. Computations were as follows:

Forearm Blood Flow

The forearm blood flow (FBF) is measured in ml per minute per 100 grams of forearm, calculated from the following formula: FBF = 2 × slope (early) × chart speed × calibration constant/L_o, where L_o is the resting arm circumference and the calibration constant is determined after the run.[1]

Capillary Filtration Coefficient

The capillary filtration coefficient (CFC) is measured as the ml per minute per 100 grams of forearm filtered through the vascular surface into the interstitium per millimeter of mercury pressure rise in the capillary, and is calculated as: CFC = 2 × slope (late) × chart speed × calibration constant × $(1+R_v/R_a)/(40\times L_o)$ where R_v/R_a is the postcapillary to precapillary resistance ratio and is assumed to be 0.25.[9] Changes in the capillary filtration coefficient measurement are insensitive to errors in the selection of this ratio.[8] Moreover, an error analysis done in our laboratory indicates that capillary filtration coefficient underestimates the true hydraulic-conductivity surface area of the vascular bed by about 0.6%, with a maximum error of −14.6%.[8]

Venous Capacity at 40 mm of Mercury Cuff Pressure (VC_{40})

This is a time-independent measure of venous capacity at a cuff pressure of 40 mm of mercury and is calculated as follows: $VC_{40} = 2 \times h \times$ calibration constant/L_o, where h is the altitude on L_o at the instant of cuff inflation to the extrapolated tangent to the filtration curve.[1]

Data are shown ± one standard error of the mean. Statistical comparisons from period to period and from treated to untreated arms were accomplished by two-way analysis of variance or paired *t* testing, or both, and by Pearson correlation coefficient analysis. These analyses were done on a CDC-6400 computer that uses a statistical package for social sciences.*

Results

Effects of Iontophoresis on Blood Pressure and Patient Well-being

Systolic blood pressure immediately before iontophoresis to the end of the interrupted repetitive exercise rose slightly from 118±2 mm of mercury to 122±3 mm of mercury, but this was not a significant change. There was a significant fall in diastolic pressure from 79±2 to 71±2 mm of mercury ($P<.001$). The slight rise in mean systolic pressure and the fall in diastolic combined to produce a mean blood pressure that changed only slightly and not significantly from 87±2 to 85±2 mm of mercury. The heart rate rose slightly but not significantly from 85±3 to 89±3 beats per minute.

Study subjects said they felt somewhat lightheaded, jittery and rarely nauseated. Some wished to remain at the laboratory for an hour after testing but then were able to return to work. Arm color was fully back to normal within six to eight hours.

Effects on Forearm Blood Flow and Conductance

Because the blood pressure did not change, alterations in forearm blood flow rather than changes in conductance were analyzed in order to decrease the random error of the data. Figure 2 shows the results of the analysis of the changes in forearm blood flow. In all three states—at rest, during tonic exercise and after interrupted repetitive exercise—the treated or muscle-only arm had 60% to 70% of the total flow or total conductance of the forearm and, in general, the muscle values correlated with the muscle-plus-skin values. With

*Mr John Gaines of the Biostatistics Division of the University of Arizona College of Medicine assisted in data analysis.

tonic exercise the muscle conductance rose about 55% and skin conductance rose about 110%. The results following interrupted repetitive exercise were even more dramatic, with muscle conductance rising about 170% and skin conductance about 340% above control.

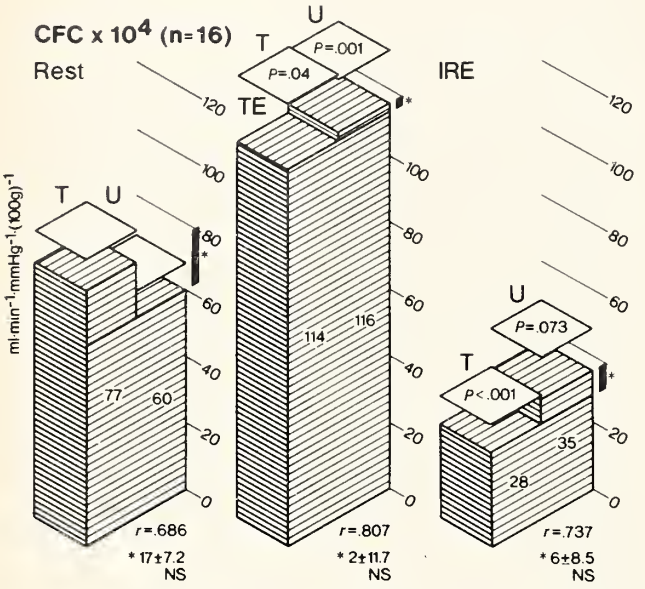

Figure 3.—Vascular or capillary filtration coefficient (CFC) results of treated arms (T) compared with untreated arms (U) at rest, during tonic exercise (TE) and after interrupted repetitive exercise (IRE). The plates represent one standard error of the mean. The solid bars with the values given after an asterisk represent the values and significance of differences between T and U; the *P* values on the plates represent the significance of differences from control, and the *r* values are the Pearson correlation coefficients between T and U. T and U have the same CFC at rest and during exercise. Note that CFC decreases with IRE. NS = not significant.

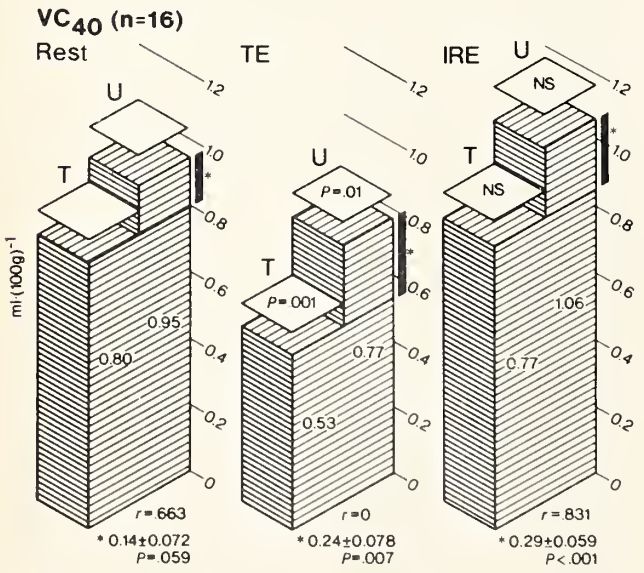

Figure 4.—Results of venous capacity at 40 mm of mercury cuff pressure designated VC_{40}. (The abbreviations are the same as for Figures 2 and 3.) See text for analysis.

Effects on Capillary Filtration Coefficient

The results of the capillary filtration coefficient were qualitatively entirely different from those of conductance, as shown in Figure 3. First, there were no significant differences between values for the treated and untreated arms during any exercise. In addition, as we have reported before,[1] tonic exercise produced about a 95% increase in capillary filtration coefficient. After interrupted repetitive exercise, however, the time when conductance was up more than threefold, the capillary filtration coefficient had fallen 55% below resting levels. The correlation coefficient between treated and untreated arms was high.

Effects on VC_{40}

At rest, the mean muscle VC_{40} (Figure 4) is about 84% of the muscle-plus-skin arm, but the difference is of only borderline significance. Correlation between muscle and muscle-plus-skin arm values was high. During tonic exercise, however, muscle VC_{40} was reduced, but because the value for skin did not change significantly, the value for muscle-plus-skin arm fell only because its muscle component had fallen. With constriction of muscle veins but not of skin veins, the correlation between treated and untreated arms vanished. With interrupted repetitive exercise, the muscle VC_{40} returned to control values, with no change in skin VC_{40}, so that untreated and treated arm values returned to control levels and regained their correlation with each other.

Discussion

By using epinephrine iontophoresis it has been possible to eliminate skin blood flow in a treated arm and hence to separate the forearm plethysmographic curve following venous occlusion into its skin and muscle components. We have assumed for the calculations that both arms should have the same resting values, and because we always treated the dominant arm of a patient—a maneuver that would minimize the differences between treated and untreated arms—the assumption seems to be reasonably adequate. In preliminary studies testing one arm before and after treatment, we found, as Cooper and associates[6] did, that systemic epinephrine effects frequently produced such changes in blood pressure that adequate analysis in a sequential study was rendered impossible.

Several conclusions are evident. Forearm muscle conductance is about 60% to 70% of total conductance and is positively correlated with conductance in an untreated or muscle-plus-skin forearm during rest and exercise. With standard exercise, muscle conductance rises to 1½ to 2½ times resting level and skin conductance rises to 2½ to 4½ times resting level.

Vascular filtration surface, the major variable of capillary filtration coefficient measured by plethysmography, is almost entirely in the muscle. It doubles in value with tonic exercise but—as we have reported

previously—falls to half its resting value after interrupted repetitive exercise despite considerable increases in conductance. Thus, repetitive exercise-induced dissociation between conductance and filtration surface occurs in the striated muscle of the forearm. Possible mechanisms for this unexpected dissociation include circulatory redistribution, lymphatic recruitment, rises in interstitial hydrostatic pressure and a number of other causes. Unpublished results of studies in dogs in our laboratory in which polyethylene capsules were used to measure interstitial pressure rule out a rise in this variable as a cause for the dissociation.

The most important conclusion to be noted from these studies is that little filtration occurs in the forearm skin. Apparently epinephrine iontophoresis is not necessary for measuring capillary filtration coefficient in the forearm striated muscle where it chiefly occurs. This renders forearm plethysmography very useful in assessing filtration in muscle. The results also indicate that the hydrostatic or pitting edema of such states as congestive heart failure may occur in the subcutaneous fat layer rather than in the skin.

Finally, muscle VC_{40} at rest and during interrupted repetitive exercise is unchanged and is about 73% to 84% of the value for skin plus muscle together. During tonic exercise there is selective muscle venoconstriction, probably by passive means, which disrupts the correlation between muscle and muscle-plus-skin values.

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Articles to Read in Other Journals

Anterior Cruciate Deficient Knee—Editorial

Hughston JC
American Journal of Sports Medicine
11:1-2, No 1, 1983

DISCIPLINE: Orthopedic Surgery

READABILITY: Very good

Jack C. Hughston, MD, has made a critical commentary on the term "anterior cruciate deficient knee." Again, this is an editorial of import to primary physicians and orthopedists who are attempting to evaluate and advise patients with acute knee injuries and chronic knee problems. This editorial defines one of the controversies arising in orthopedic surgical treatment today.

DUANE M. KLINE, MD
Cheyenne, Wyoming

Clinical Investigation

Effects of Nonsteroidal Antiinflammatory Drugs in Conventional Dosage on Glucose Homeostasis in Patients With Diabetes

NANCY L. MORK, RNP, *and* R. PAUL ROBERTSON, MD, *Seattle*

Larger-than-conventional doses of nonsteroidal antiinflammatory drugs (NSAIDs) are known to lower plasma glucose levels. This phenomenon has raised the questions whether or not NSAIDs in conventional dosage can be used for the treatment of hyperglycemia in patients who have non-insulin-dependent diabetes mellitus and whether or not NSAIDs added to preexistent hypoglycemic drug therapy taken orally may lead to unanticipated hypoglycemia. In this study we evaluated aspirin, sodium salicylate and ibuprofen given in conventional dosage to hyperglycemic patients with adult-onset (type II) diabetes. Half the patients were usually treated for hyperglycemia by means of diet only and half with diet plus hypoglycemic drugs given orally. Significant changes in plasma glucose levels were not seen after the administration of a combination drug containing aspirin and magnesium-aluminum hydroxide (Ascriptin, 650 mg three times a day; glucose change = 236±30 to 236±31 mg per dl) or sodium salicylate (600 mg three times a day; glucose change = 284±76 to 273±84 mg per dl). A statistically significant but small change was seen with the administration of ibuprofen (600 mg three times a day; glucose change = 196±60 to 179±47 mg per dl) but not when giving ibuprofen (300 mg three times a day; glucose change = 267±78 to 282±60 mg per dl). The results of this study indicate that conventional doses of NSAIDs should not be used for treating hyperglycemia and that, since the additive hypoglycemic effect of NSAIDs in conventional doses was minimal or negligible, they can be used safely for other purposes in diabetic patients taking hypoglycemic drugs orally.

The first observation that a nonsteroidal antiinflammatory drug could enhance carbohydrate tolerance in patients with diabetes mellitus was made by Ebstein in 1876.[1] He showed that sodium salicylate given orally would decrease the amount of glucose excreted in the urine of diabetic patients. Subsequently, other investigators reported that nonsteroidal antiinflammatory drugs could improve carbohydrate tolerance in diabetics.[2,3] In 1971 these drugs were discovered to inhibit prostaglandin synthesis.[4,5] At about the same time, certain prostaglandins, particularly prostaglandins of the E series, were found to inhibit glucose-induced insulin secretion in animals[6-8] and in humans.[9-11] The studies of Robertson and Chen[12] showed that intravenous infusions of sodium salicylate in patients with adult-onset diabetes could partially restore previously absent glucose-induced acute insulin responses and improve glucose disappearance rates after the intravenous administration of glucose.

Because of these investigative findings, questions have been raised by clinicians about the use of nonsteroidal antiinflammatory drugs as therapeutic agents

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Submitted, revised, January 13, 1983.

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in diabetic patients. One of these questions is whether or not nonsteroidal antiinflammatory drugs can be used to help regulate glycemia in patients with non-insulin-dependent diabetes mellitus. Another is whether or not adding a nonsteroidal antiinflammatory drug to an established therapeutic regimen of oral hypoglycemic agents in diabetic persons might lead to unanticipated hypoglycemia because of additive drug effects. These issues cannot be addressed from available data because previous studies for the most part have used higher-than-conventional doses of nonsteroidal antiinflammatory drugs for only brief periods. The studies described herein were designed to evaluate the effects on glucose homeostasis of conventional doses of several nonsteroidal antiinflammatory drugs used for extended periods in persons with non-insulin-dependent diabetes.

Patients, Materials and Methods

Patients

All patients studied had type II (adult-onset) diabetes mellitus and fasting hyperglycemia. Their usual therapy consisted of dietary measures only or dietary measures plus conventional hypoglycemic therapy taken orally. No one was treated with insulin. A total of 58 men and 19 women was studied; ages ranged from 38 to 78 (58±9; mean±standard deviation). All studies were done in the Outpatient Department of the Seattle Veterans Medical Center where careful attention was given weekly to monitoring compliance in drug treatment, symptoms and levels of circulating glucose.

Treatment Protocols

Group I. A total of 77 patients was randomly assigned to one of four drug subgroups: aspirin (Ascriptin [a combination drug in which each tablet contains aspirin, 325 mg, and magnesium-aluminum hydrochloride, 150 mg], 650 mg taken orally three times a day); sodium salicylate (600 mg taken orally three times a day); ibuprofen (300 mg taken orally three times a day), and a placebo taken by mouth three times a day. The drug subgroups to which the patients were assigned were unknown to them and to the investigator managing the patients. There was an initial two-week drug withdrawal period during which all drugs known to affect carbohydrate tolerance were withheld from the patients. This was followed by a 12-week period during which either a nonsteroidal antiinflammatory drug or a placebo was given to the patients. During the last eight weeks of this 12-week period, those patients who normally were treated with oral hypoglycemic agents were asked to resume taking these drugs in addition to their other regimen.

Group II. This study further evaluated the effects of ibuprofen, 600 mg taken orally three times a day, and a placebo. There was no initial drug withdrawal period; instead, subjects were allowed to continue with their usual pretrial oral hypoglycemic therapy, if any. A double-blind crossover design was used in which 24 of 48 persons began taking ibuprofen while the other half began taking a placebo. The duration of this drug trial was eight weeks and patients crossed over to the alternate regimen (ibuprofen or placebo) at the end of the fourth week.

Measurements

During these drug trials measurements were made of fasting plasma glucose and insulin levels. Glucose tolerance tests were done intravenously in some patients to determine glucose-induced acute insulin responses and glucose disappearance rates. All of these studies were carried out using conventional and standard techniques.[9] Statistical analyses were done using the Wilcoxon matched-pairs ranks test.

Results

Group I

Ascriptin, sodium salicylate, ibuprofen and placebo. The results from measuring fasting plasma glucose

TABLE 1.—*Fasting Plasma Glucose Levels in 50 Persons With Type II (Adult-Onset) Diabetes Before and During Treatment With a Nonsteroidal Antiinflammatory Drug (NSAID) Only for 4 Weeks, Then During Treatment With an NSAID Plus Usual Diabetic Drug Therapy (If Any) for 8 More Weeks**

Drug Group and Subgroups (Number of Persons)	*Fasting Plasma Glucose (mg/dl) Levels (mean ± SD)*				
	Pretrial	*After 2 Weeks Drug Withdrawal*		*After 4 Weeks NSAID Only*	*After 8 Weeks NSAID Plus Usual Therapy*
Ascriptin (11)	193±62	236±30	($P<.01$)‡	236±31	232±30
Diet only (7)	175±61	198±97		187±82	200±107
Oral agent (4)†	222±58	302±66		321±77	289±61
Sodium salicylate (14)	205±51	284±76	($P<.005$)‡	273±84	233±57
Diet only (7)	203±54	272±84	($P<.025$)‡	225±59	210±62
Oral agent (7)	208±51	296±72	($P<.01$)‡	321±80	256±44
Ibuprofen (14)	203±57	267±78	($P<.005$)‡	282±60	241±61
Diet only (7)	217±58	281±100	($P<.025$)‡	272±70	265±70
Oral agent (7)	189±58	253±51	($P<.01$)‡	293±51	217±43
Placebo (11)	206±54	264±69	($P<.005$)‡	273±74	258±69
Diet only (6)	193±53	228±36	($P<.025$)‡	230±43	239±50
Oral agent (5)	222±56	308±78		324±74	280±87

SD=standard deviation

*Doses used were: Ascriptin (each tablet contains aspirin, 325 mg, and magnesium-aluminum hydroxide, 150 mg), 650 mg 3 times a day; sodium salicylate, 600 mg 3 times a day, and ibuprofen, 300 mg 3 times a day.
†The term "oral agent" refers to the use of any conventional hypoglycemic drug given orally.
‡*P* values as compared with pretrial values.

levels in the four groups of persons with diabetes are presented in Table 1. Of 77 patients, 50 completed the study. Fasting plasma glucose levels generally rose by the end of the two-week period during which all drugs known to affect glucose homeostasis were withdrawn from the patients. This occurred at a statistically significant level in each of the four groups. This observation was also made in five of the subgroups, in three of which the patients had not been receiving oral hypoglycemic agents before the pretrial fasting glucose level had been measured. There were no statistically significant falls in fasting plasma glucose levels in any of the subgroups after they had been treated four weeks with a nonsteroidal antiinflammatory drug or a placebo. Comparisons of the pretrial levels and the levels that occurred after the final eight weeks, during which a nonsteroidal antiinflammatory drug plus the usual hypoglycemic therapy was given orally, failed to show any significant differences. The only adverse drug effect occurred in one patient taking ibuprofen in whom a rash developed that disappeared when the drug was discontinued.

Group II

Ibuprofen-placebo crossover without a period of hypoglycemic drug withdrawal. Results of measurements from the persons participating in this study are given in Table 2. Of 48 patients, 37 completed the study. Significant decrements in plasma glucose levels occurred only in the persons receiving ibuprofen who were also receiving their usual oral hypoglycemic therapy. This occurred in both groups whether the placebo or ibuprofen was given for the first four weeks. In contrast, no glucose lowering was observed in the groups receiving ibuprofen who were normally treated with dietary measures only. Glucose decrements were also seen when data from both the patients who normally received oral hypoglycemic agents and the patients who normally were treated with management of diet only were pooled if ibuprofen had been given before the placebo. However, this effect of ibuprofen was not noted when the data from the groups receiving the placebo first were pooled. No significant changes occurred in fasting plasma insulin level in either of the two groups or the four subgroups. Because of the limited number of persons having intravenous glucose tolerance testing, the data from persons normally treated with diet only and diet plus hypoglycemic drugs taken orally were pooled. There was no significant alteration in glucose-induced acute insulin responses or in glucose disappearance rates in these subjects. There were no adverse drug effects.

Discussion

These studies were undertaken to assess whether or not conventional doses of commonly used nonsteroidal antiinflammatory drugs cause clinically significant falls in fasting plasma glucose levels when given to persons who have type II diabetes with fasting hyperglycemia. The usual treatment of diabetes before this study for about half of the patients consisted of dietary measures only; the other half were also taking hypoglycemic agents orally, usually either tolbutamide or chlorpropamide. The persons in group I received either aspirin, sodium salicylate, ibuprofen or placebo. For two weeks before the start of the 12-week drug ingestion period, all were asked to discontinue taking their oral hypoglycemic agents, if any. There was a uniform trend in all groups for fasting plasma glucose levels to rise during this two-week "washout" period. Interestingly, the tendency for hyperglycemia to develop was noted not only in the patients who had been using hypoglycemic agents but also in those who had been using dietary measures only. The meaning of these occurrences is not

TABLE 2.—*Fasting Plasma Glucose Level, Fasting Plasma Insulin Level, Acute Insulin Response and Glucose Removal Rate in a Randomized Double-Blind Crossover Study of Persons With Type II (Adult-Onset) Diabetes (N=37)**

	Diet Therapy Only (13)			*Diet Therapy Only (9)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	245±72	244±75	245±71	176±58	165±48	181±59
Fasting plasma insulin (μU/ml) ...	16±10	10±5	13±10	15±12	17±15	15±13
	Diet + Oral Agent (7)			*Diet + Oral Agent (8)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	261±15	268±53	223±64 ($P<.01$)†	218±57	194±45 ($P<.01$)†	200±54
Fasting plasma insulin (μU/ml) ...	22±14	14±9	12±6	24±21	19±12	18±11
	All Patients (20)			*All Patients (17)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	251±58	252±68	237±68	196±60	179±47 ($P<.005$)†	190±56
Fasting plasma insulin (μU/ml) ...	18±12	12±7	12±8	19±17	18±14	17±12
	All Patients (4)			*All Patients (7)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Acute insulin response (%)‡	95±15	91±19	80±13	90±35	106±28	80±14
Glucose removal rate (mg/dl a min)	.31±.26	.31±.16	.32±.21	.67±.34	.51±.11	.55±.14

*Some subjects received placebo for 4 weeks, then ibuprofen, 600 mg 3 times a day, for 4 weeks; the rest received ibuprofen for 4 weeks, then placebo for 4 weeks. Numbers in parentheses indicate the number of persons in each group and subgroup. Data are presented as mean ± standard deviation.

†Compared with pretrial values.

‡Percentage of basal fasting plasma insulin level.

clear but they suggest that some of the persons were less rigorous in their dietary measures during the washout period than they had been before the initial specimens for fasting plasma glucose levels were collected.

During the 12-week period when a nonsteroidal antiinflammatory drug or placebo was given, there was no evidence in any of the drug subgroups of a diminution of fasting plasma glucose levels. Even during the last eight weeks when about half the patients had resumed taking their usual diabetic therapy with oral hypoglycemic agents, there was no evidence that glucose levels were less than those at the beginning of the study before the drug withdrawal period. Consequently, it can be concluded that none of the three nonsteroidal antiinflammatory agents was adequate for treating hyperglycemia without the use of hypoglycemic agents. Moreover, a combination of oral hypoglycemic agents and nonsteroidal antiinflammatory drugs did not cause symptomatic or measurable hypoglycemia.

The persons in group II received a twice higher dose of ibuprofen and the placebo in a double-blind crossover manner. There was no withdrawal of hypoglycemic drugs before these studies; instead, the nonsteroidal antiinflammatory drug or placebo was simply added to a patient's usual therapeutic regimen for control of hyperglycemia. This trial was conducted because of the possibility in the first trial that deterioration of glucose homeostasis during withdrawal of oral hypoglycemic agents from group I might have masked slight glucose-lowering effects of nonsteroidal antiinflammatory drugs. In the subgroups of patients in group II who were usually treated with oral hypoglycemic agents, adding ibuprofen caused a further fall in circulating glucose levels whether it or the placebo was the first agent used during the trials. In contrast, this effect of ibuprofen did not occur in patients whose normal therapeutic regimen for diabetes consisted of dietary measures only. Consequently, it can be concluded only that adding ibuprofen to a therapeutic regimen of oral hypoglycemic agents may further lower circulating glucose levels. This did not occur to a great extent, however, and in no instance did any person have symptoms of hypoglycemia. The mechanism of this additive drug effect was not pursued in this study but possibilities include inhibition of cyclooxygenase as well as displacement by ibuprofen of albumin-bound oral hypoglycemic agents in circulation.

The data collected relating to glucose-induced insulin responses and glucose disappearance rates failed to show any significant effects of ibuprofen therapy. This is in contrast to prior observations of beneficial effects of nonsteroidal antiinflammatory drugs and ibuprofen specifically on acute insulin responses and glucose disappearance rates.[9-12] It should be recalled, however, that in the studies cited higher doses of a nonsteroidal antiinflammatory drug were usually used (for example, sodium salicylate infusions at 40 mg per minute given intravenously achieved serum salicylate concentrations of more than 25 mg per dl[9] compared with 600 mg by mouth three times a day in this study, which failed to cause detectable levels in serum) and normal persons instead of those with diabetes were used for the ibuprofen trials.

Conclusion

We can conclude from our studies that nonsteroidal antiinflammatory drugs may be used safely for control of symptoms of an inflammatory condition in combination with oral hypoglycemic agents. Nonsteroidal antiinflammatory drugs should not be considered as therapy for hyperglycemia. They are very useful tools, however, for research about diabetes in humans and for in vitro laboratory research. In this context, if the hypothesis is correct that the beneficial effects of larger-than-conventional doses of nonsteroidal antiinflammatory agents on glucose homeostasis in patients with diabetes are related to inhibition of cyclooxygenase activity and augmented insulin secretion,[13] then an evaluation of this class of agents for the treatment of hyperglycemia must await the development of future generations of drugs that are highly specific for pancreatic islet cyclooxygenase. Drugs such as these will need to affect pancreatic islets but not other tissues wherein inhibition of cyclooxygenase may lead to undesirable effects.

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Inadequate Medical Order Writing

A Source of Confusion and Increased Costs

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Audits of medication and intravenous fluid orders and of return to the pharmacy of unused intravenous solutions were conducted in 1980 at a university teaching hospital in response to a prevailing impression among pharmacists that physicians' orders were often written in an incomplete, nonstandardized fashion and that intravenous fluid wastage was common. A disturbing number of orders were incomplete and judged to be ambiguous. Less than 25% of orders for intravenously given solutions contained adequate instructions for subsequent administration of fluids. Intravenous fluid return amounted to an estimated loss of $137,695 per year in wasted material and labor.

The results of the audits were disseminated among the staff. In addition, the pharmacy changed its operations to detect more quickly and correct the problems caused by ambiguous orders. Later studies showed a reduction in the return of unused intravenous fluids and some improvement in order writing. Inadequate and ambiguous orders were still judged to be a problem, however, especially intravenous fluid orders that omitted instructions for subsequent fluid requirements and "open-ended" intravenous fluid orders. Such orders were eight times more likely to be associated with return of unused intravenous fluids than orders with adequate instructions for giving fluids subsequently.

An important source of rising health care costs is inefficiency in the use of so-called little ticket technologies.[1] "Little ticket" refers to the thousands of tests and procedures that are used most frequently by physicians and that individually cost little. By contrast, a "big ticket" technology such as computerized tomographic scanning is very expensive and, therefore, attracts a great deal of attention. According to Moloney and Rogers,[1] however, the "big tickets" account for far less of the escalating cost of medical care than do the cumulative costs of "little ticket" activities common to everyday medical practice.

Hospital costs account for a substantial portion of all personal health care expenditures. In 1981 hospital costs amounted to $112.3 billion out of the $278.5 billion spent for personal health care in the United States.[2] In hospital, big and little ticket technologies are administered through a variety of means, one of which is a physician's order.

The process of medical order writing is an instrumentally important activity for using hospital resources, especially drugs and intravenously given fluids. In our hospital, charges for pharmacy services accounted for 5.4% of patient charges in 1981. Nationwide in 1981 $20.6 billion were spent on drugs and medical sundries (inpatient and outpatient).[2] Thus, we were concerned when pharmacists noted that orders for drugs and intravenous fluids were often incomplete and ambiguous. They also suspected that substantial amounts of intravenous fluids were returned unused to the pharmacy, possibly as a consequence of inadequate, nonstandardized orders. Because of this prevailing impression, an audit was done in 1980 to assess the quality of medication and intravenous orders and to determine the amount of return and waste of intravenous solutions. The results of the original 1980 studies led to changes in pharmacy policy and to follow-up studies of the quality of order writing and the "causes" of intravenous

Refer to: Larson EB, Scott DH, Kaplan HG: Inadequate medical order writing—A source of confusion and increased costs (Clinical Investigation). West J Med 1983 Jul; 139:50-54.

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fluid wastage. The follow-up studies showed a reduction in the losses due to wasted materials. Herein we describe our studies of this "little ticket" activity that is of great importance to the efficient operation of a modern hospital.

Methods

The process of order writing and delivery consists of at least the following four phases:

1. *Order writing.* A physician writes an order.

2. *Charting and distribution.* A ward clerk notes the order and distributes it to nursing and pharmacy departments, where it is reviewed and filed in the respective patient's chart.

3. *Preparation and delivery.* A centrally based pharmacist prepares or obtains the medication or intravenous solution ordered and has it delivered to the nursing unit.

4. *Administration.* Nursing staff administers medication and intravenous fluids to the patient.

Although problems may arise in any phase, we studied the first and fourth elements of this process: medication order writing and whether intravenous fluids were administered or returned unused, a short-term outcome of the entire process.

Criteria for the adequacy of a medication order were established by a group comprised of two physicians, a nurse and a pharmacist. The group selected a set of criteria designed to yield an order that was unambiguous, that could be acted upon with the least possibility of error and that could be prepared without delays or extra steps required, such as telephone calls for clarification. Another goal of the criteria was that adequate orders would not be a source of waste. The criteria specified that each medication order should include the following elements: (1) medicine—the generic name is specified and is unabbreviated; (2) dose; (3) route of administration; (4) frequency of administration, and (5) whether or not the order is a PRN *(pro re nata,* "according to circumstances" or "as needed") order. Criteria for orders for intravenous solutions were similar, specifically that an order should contain the following elements: (1) solution name, (2) volume of solution, (3) concentration of additives, (4) rate of administration and (5) orders for subsequent fluids.

Statistics were also kept on other elements that the group felt were necessary for completeness and for efficient pharmacy operations including whether or not the date and time of the order and location of the patient were given and the legibility of the signature. Because these elements were not formal criteria, orders that did not meet these criteria were not reviewed separately.

The order-writing sample consisted of all medication and intravenous fluid orders written during a randomly selected 24-hour period in 1980 and in 1981. The 24-hour period selected for study was unknown to members of the hospital staff, except those doing the study. The orders were reviewed by trained abstractors for compliance with the above criteria. Each order that did not meet the criteria was reviewed by two physicians and a pharmacist to determine if it was ambiguous, might cause errors or delays and might lead to waste.

TABLE 1.—*Compliance With Adequacy Criteria of Physicians' Written Orders*

Adequacy Criteria	*Rate of Compliance*	
	1980 Percent	*1981 Percent*
Medication	(n=639)	(n=865)
Dose given	93.6	92.7
Route of administration given	88.1	90.0
Frequency stated	87.8	87.9
Indication for PRN order	54.0* (n=226)	83.0* (n=276)
Intravenous Fluids	(n=75)	(n=119)
Name of solution given .	94.7	92.4
Volume stated	52.0	37.0
Rate of infusion given ..	84.0	87.4
Instructions for subsequent administration of fluids included	24.0	28.6

PRN=*pro re nata,* "according to circumstances" or "as needed."

*$P<.001$ by x^2.

The return of unused intravenous (IV) fluids was determined by keeping a record of all intravenous solutions returned unused to the pharmacy for 72-hour periods. The original study of IV fluid return (March 5 through 7, 1980) was supplemented by two follow-up studies after the pharmacy changed operations. A restudy of return was done in 1981, about a year after the original audit. Costs associated with intravenous solutions were calculated on the basis of the actual cost to the pharmacy of materials not used and the cost of preparation time. To calculate the cost of preparation time, we observed the time required to prepare intravenous solutions and, based on the pharmacists' wages, the cost of time spent preparing solutions that were unused. Average preparation times were 5 minutes per intravenous solution order, 2.5 minutes for "piggyback" intravenous solutions (a medication preformulated in a 25- to 100-ml container, which is then connected to an already running intravenous solution bottle) and 40 minutes for a total parenteral nutrition solution. Costs were calculated on the basis of 1980 material costs and wages. The 1981 restudy of unused intravenous fluid included a detailed analysis of the reasons for return of the fluids. The type of order and the reason the fluid was returned unused to the pharmacy were determined by reviewing the circumstances associated with each unit of solution returned. Comparisons were tested for statistical significance using the x^2 test and Yates' continuity correction.[3]

Results

In all, 725 medication orders (including 86 "stop" orders) were written during a 24-hour study period in 1980 and 967 (including 102 "stop" orders) in 1981. A substantial number of orders did not meet the study criterion of containing an unabbreviated generic name

(57.4% in 1980, 50.6% in 1981). Reviewers did not consider this a source of confusion, however, except when abbreviations or other ambiguous names were used. Examples included: "iron," "chloro"' and "tyl."

Table 1 shows the rates of compliance with order-writing criteria for the initial medication and intravenous fluid orders. Orders written without a specific dose were not a major problem because 90.2% (37 of 41) either were available in only one dosage form or the dose could be determined from previous orders or written intensive-care-unit protocols. Of about 10% of medication orders not stating route of administration, 52.6% involved drugs in which different routes are possible and the orders were therefore ambiguous. Examples encountered included heparin, furosemide, diazepam, morphine sulfate, meperidine hydrochloride, propranolol and potassium chloride.

Physicians reviewing noncompliant orders and selected charts found no evidence that orders that did not specify frequency resulted in adverse outcomes to patients. However, such orders did transfer interpretation and decision making to nursing staff, posed problems for the pharmacy filling these orders and increased the likelihood of error. Almost half of the PRN orders analyzed in the 1980 study did not state the indications for need. The reviewers noted instances when PRN orders were ambiguous because the medication might have various indications. Examples included orders for diazepam in patients with seizures and those for acetaminophen in neutropenic patients receiving cancer chemotherapy.

Table 1 also shows that orders for intravenous fluids written during the same 24-hour period often did not meet the criteria for an adequate IV order. The inadequacies, taken individually or as a whole, were judged to create ambiguities for both nurses and pharmacists. Orders that did not specify volume created a major problem when they included an additive, which made the desired concentration indeterminate. Orders that did not state the rate of flow caused difficulty both for pharmacists who prepared and delivered the solutions and for nurses who administered them.

The frequency with which an order for subsequent administering of IV fluids was stated was only 24% in 1980 and 28.6% in 1981 (Table 1). In our hospital, the absence of specific instructions for subsequent administration of fluids is a major problem and a source of waste, because intravenous solutions are formulated in the pharmacy, not on the wards. Any order without a "to follow" instruction is assumed to be a continuous order—that is, to be continued indefinitely until a discontinue order is written. The high frequency of orders without specific instructions for subsequent intravenous administration of fluids was considered to be a serious problem detected by this study and an important cause of the return of unused IV solutions to pharmacy.

In the 1980 audit, the high frequency of illegibility of signatures and of orders in which the nursing unit was not stated (Table 2) was judged by reviewers to create problems, especially when ambiguous orders were received and a pharmacist must attempt to find the physician or the origin of that order. In the 1981 audit, signatures were more frequently legible (P less than .001) and the nursing unit was noted on virtually all orders.

TABLE 2.—*Items That Contribute to Efficiency of Medication and Intravenous Fluid Orders*

Miscellaneous Items	Rate of Compliance: 1980 (n=300) Percent	Rate of Compliance: 1981 (n=429) Percent
Signature legible	49.0*	82.1*
Date given	85.3	90.0
Time given	20.7	31.0
Nursing unit stated	83.6*	98.8*

*$P<.001$ by x^2.

TABLE 3.—*Description of Intravenous Solutions Returned to Pharmacy Unused**

	1980 Number (Percent†)	1981 Number (Percent†)
Intravenous solutions returned per day	50.0 (46.7)‡	25.7 (26.6)‡
Piggyback intravenous solutions returned per day	47.0 (18.4)§	20.3 (9.5)§
TPN solutions returned per day	1.0 (3.7)	0.3 (1.5)
Cost per day of material	$302	$135
Preparation time per day (hours)	6.8	3.1
Estimated cost per year of wasted material and labor	$137,695	$63,488

TPN = total parenteral nutrition.

*Based on a 72-hour period in 1980 and a 120-hour period in 1981.
†$\frac{\text{IV's returned per day}}{\text{IV's prepared per day}} \times 100$
‡$P<.001$ by x^2.
§$P<.01$ by x^2.

The results of our 1980 audit of IV solution return and waste and the 1981 restudy are shown in Table 3. During the 1980 study period, 46.7% of 321 IV solutions prepared in a three-day period were returned, 18.4% of 766 piggyback intravenous solutions and only 3.7% of 81 total parenteral nutrition solutions. Using patient-bed days as a denominator, 0.32 intravenous solution units per patient-bed day were returned during this survey period.

The enormous cost of wasted material and effort (Table 3) was of great concern to members of pharmacy and the medical staff. The results of these 1980 studies were circulated to medical staff, house staff and pharmacy staff.

After the audit results were disseminated, the pharmacy changed its operation to decrease the amount of time a problem perpetuates itself due to ambiguous information or lack of information. Specifically, IV solutions are now prepared four times a day instead of once a day. Before intravenous solution units are sent to a floor (five times per day), the admission, discharge and transfer information sheets are checked. Every delivery made by pharmacy technicians now includes a check for discontinued solutions and the accumulation of piggyback intravenous bottles on the ward so that

TABLE 4.—*Some Causes of Return of Unused Intravenous Solutions*

	Number (n=231)	*Percent*
Manner in which intravenous solution order is written	64	27.7
Manner in which order is interpreted or acted upon on the ward	94	40.7
Manner in which pharmacy acts on orders	37	16.0
Admission-discharge transfer problems	19	8.2
Indeterminate	17	7.4

when an intravenous solution regimen is discontinued, the pharmacy is informed sooner. (Formerly the pharmacy computer continued to print labels until the pharmacy was notified that an order had been discontinued.)

In two follow-up surveys in 1980 (not displayed in the table) we recorded a progressive reduction in the return of intravenous solutions. A month after the pharmacy changed its operations, 34.0% of IV solutions, 8.0% of piggyback intravenous bottles and 2.8% of total parenteral nutrition solutions were returned. A survey one month later found that 20% of intravenous solutions and 8.0% of piggyback IV units were returned per day.

In 1981, about a year after the original study, we restudied the frequency of return of intravenous preparations. As shown in Table 3, the reduction observed in 1980 persisted, but substantial amounts of IV fluids were still being returned unused to the pharmacy. In the 1981 study, 0.16 intravenous fluid units per patient-bed day were returned unused.

The 1981 IV return study included a more detailed analysis of 231 intravenous fluid units returned during a five-day period (Table 4). The specific cause for return of intravenous solutions could be determined for 92.6% of all those returned; in 27.7% the cause for the unused IV fluid return was considered directly related to the manner in which the order was written. When IV return was related to actions that occurred on the ward (94 instances), the most common reason was that the IV solution was not given as ordered (27 instances). Of 37 intravenous solution units returned due to pharmacy-related causes, 24 were related to the pharmacy's intravenous fluids delivery schedule. Of the orders associated with solutions returned unused, 96.6% did not contain adequate instruction for giving subsequent fluids. Of orders without adequate instructions for subsequent fluids, 81.2% were "open-ended."

Discussion

Our findings were that medication orders and orders for intravenously given fluids were frequently incomplete. Incomplete orders are ambiguous and typically lead to an error in medication administration, require time-consuming telephone calls for clarification or simply transfer patient-care decision making to nonphysicians. Incomplete and ambiguous orders create special problems for pharmacists who formulate and prepare orders centrally, especially when they have difficulty locating the physician who wrote the order.

The enormity of IV solution waste was surprising. Because we could find no reports of the magnitude of return of unused intravenous preparations in other institutions, it was not possible to determine whether or not our hospital was unusual. Nonetheless, the estimated loss was considerable and amounted to more than 20% of the pharmacy's 1980 intravenous solution budget.

The inefficiency in our system appeared to be reduced when the pharmacy's operation was changed to quickly respond to changes in patient intravenous fluid requirements even in the absence of a correctly written order. The changes probably reduced waste simply by decreasing the amount of time a problem perpetuates itself. The changes involved restructuring pharmacy staff work procedures and did not result in added staff or costs. Despite these changes, however, waste of intravenous fluids still occurs.

The reasons for IV solution return and waste are complex. In the 1981 study we identified 19 different causes for return of intravenous fluids, suggesting that a certain amount of waste is inevitable given the changing needs of patients and the complexity of a modern hospital. A prominent cause of special relevance to physicians was the open-ended IV order. In this study, an order written without instructions for subsequent intravenous administration of fluids was more than eight times more likely to be returned than an order that included such instructions, suggesting that more careful order writing would reduce the waste. We believe that intravenous fluid orders should be written for only a 24-hour period. A good system is to number each intravenous solution bottle ordered as follows:

1. 1,000 ml of normal saline at 125 ml per hour.
2. 1,000 ml of 5% dextrose in half normal saline at 125 ml per hour.
3. 1,000 ml of 5% dextrose in half normal saline at 50 ml per hour.

For continuous infusion of the same solution, the duration of the infusion should be described and reordered every 24 or, at most, 48 hours. In our 1981 audit, only 4 (1.7%) of 231 IV solutions returned were ordered with those instructions. Return of unused preparations in these instances was related to unanticipated changes in patient status, an uncontrollable factor.

Most literature on medication orders and prescriptions has focused on medication errors,[4,5] illegibility of physician handwriting[6] and errors in physicians' prescriptions.[7] Our study assessed a large number of orders and found that many were incomplete. Incomplete and ambiguous orders are a source of medication error.[4] They are also a source of inefficiency when they lead to time-consuming telephone calls for clarification. Our findings, and the findings of others,[4-7] suggest that physicians, perhaps because other aspects of patient care seem to be more important, too frequently ap-

proach order writing with a casual attitude. This and any subsequent inadequacies may relate to the fact that schools and training programs typically do not systematically instruct trainees in this topic or emphasize the importance of careful order writing. Instruction usually occurs on the wards and is not standardized.

We hope that our findings will stimulate others to further investigate order writing and related topics like return and waste of intravenous solutions to determine if the findings are unique or generalizable. Most important, we hope that they will prompt physicians to exercise more care in writing orders and to educate students and physicians-in-training to approach order writing in a careful, systematic fashion.[8] A more careful approach to order writing should improve patient care and help eliminate excess health care costs associated with a physician activity that is extremely important for the efficient operation of a modern hospital.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Collagen Implants

QUESTION:

Are collagen implants considered accepted medical treatment or are they investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Dermatology and Plastic Surgery, collagen implants are considered established medical practice for the treatment of contour defects of the skin.

Collagen implant treatments have been used primarily for cosmetic reasons. The experience to date suggests the preparation is safe and useful for the temporary correction of superficial scarring resulting from acne, chickenpox, excoriations and wrinkling, in certain areas of the face. Repeated treatments are frequently necessary. The duration of the cosmetic effect is not known because of insufficient long-term experience with the preparation.

Selection of the patient requires good judgment. Clear indications for the optimal use of collagen implants and their long-term potential for allergenicity are still to be established.

Medical Progress

Chemicals, Cancer and Cancer Biology

EDWARD A. SMUCKLER, MD, PhD, *San Francisco*

Chemicals can cause cancer in humans and animals. Two significant questions are how and how frequently do these neoplasms arise? The first documentation of chemically induced cancer in humans was of the occupationally related "soot wart" in 1775. Since that time various carcinogens have been identified. Some compounds act directly on cell populations, whereas others must be metabolized by a host to produce a "proximate" or "ultimate" carcinogen. Because of the variety in carcinogen structure and the multiplicity of modifications to the cellular macromolecules, a simple explanation for chemical effect is unlikely. Furthermore, true neoplastic growth involves at least two and possibly more steps, some of which are reversible. Evidence suggests that cancer represents an altering of differentiation and that chemical agents may act at the level of DNA or on epigenetic regulatory phenomena. The method for selecting the neoplastic cell from those that are normal is not known. Because we cannot explain the mechanisms for cancer formation or the role of chemicals in the process, prudence is needed in determining the significance of human exposure and in relating this exposure to the risk of neoplastic disease.

Chemicals cause cancer in animals and humans. There is probably no issue that has become so emotionally charged as the question of the cancer risk in the population at large, or one so subject to litigation as the relationship between occupational exposure to chemicals and the occurrence of neoplastic disease in workers. We need only survey newspapers to read almost daily about environmental concerns, from contaminants in the drinking water of San Francisco to the filing of a Chapter 11 by the Manville Corporation, to realize the impact this has had on our society. Extreme points of view have emerged. In the *Politics of Cancer,* Sam Epstein predicts an epidemic of neoplastic disease due to environmental contamination.[1] At the other end of the scale is the attitude espoused by many lawyers involved in industrial suits and representatives of the tobacco industry who suggest that *no* evidence "proves" that chemicals can cause cancer. In the middle is the attitude of moderation expressed by Peto and Doll.[2]

For these reasons it is appropriate to briefly review the chemically and industrially related types of cancer, especially as they are germane to our present understanding of chemical carcinogenesis, to provide a framework for our understanding of this important and controversial issue.

Historical Precedents

Sir Percivall Pott observed an association between continued exposure to soot and the appearance of squamous carcinoma of the scrotum in chimney sweeps.[3] He also observed that cancer was the end stage of a complex process that required years to develop. In point of fact, warty growths would develop on the scrotum of a young chimney sweep but only an older chimney sweep would succumb to the disease. Pott's implication of soot as a causative agent was indirect. However, the hygienic measures he recommended, including bathing, were actually instituted by the Dutch Guild of Chimney Sweeps, resulting in the elimination of this disease on the continent.

The subsequent identification of mule spinner's disease, the development of squamous cell carcinoma on the abdomen in textile workers using shale oil, radium painter's jaw (or "mossy jaw") associated with the deposition of radioactive radium salts in bony tissues in watch-dial painters and the development of bladder

Refer to: Smuckler EA: Chemicals, cancer and cancer biology (Medical Progress). West J Med 1983 Jul; 139:55-74.
From the Department of Pathology, University of California, San Francisco, School of Medicine.
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cancer in aniline dye workers clearly indicated that some type of relationship exists between human exposure to specific chemicals and the ultimate appearance of malignant neoplasms in exposed populations.[4] It should be recalled that Emil Fischer and his student Eldon Hartshorn both died of bladder cancer, terminating lifetimes spent investigating the organic chemistry of aniline derivatives. The two most recent notable additions to this list of cancer-causing chemicals include vinyl chloride, prolonged exposure to which is associated with liver cancer, and asbestos, which is associated with mesothelial disease (Figures 1 and 2). A critical review of the international medical literature indicates that slightly more than 80 cases of vinyl chloride-associated liver cancer have been identified; the number of cases of mesothelioma associated with asbestos is probably greater, but the numbers are not so well defined.[5,6] These historical observations clearly point to the fact that cancer in humans is associated with exposure to a variety of chemicals, radiation and physical agents. Not surprisingly, the variety of experimental techniques used to induce neoplasms, benign and malignant, in animals is an outgrowth of these observations in humans. What is not known is how these chemicals cause the neoplastic disease. There are some salient features concerning the biology of cancer that need interpretation, and perhaps some definitions should be given before chemical carcinogenesis is discussed.

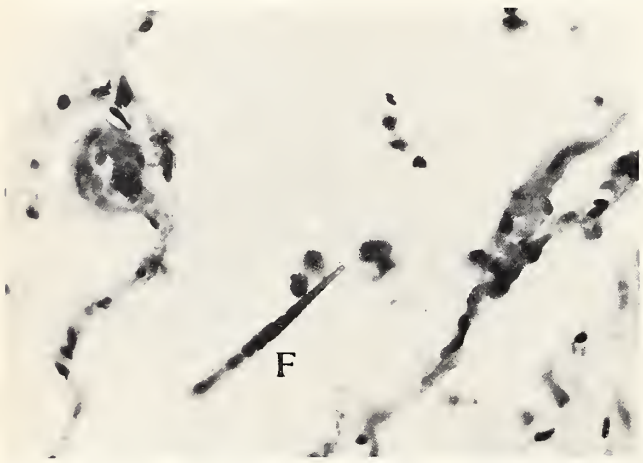

Figure 1.—Micrography of a section of lung of a shipyard worker showing an asbestos fiber coated with iron oxide **(F)**. The "ferruginous" body lies free in an alveolar space, shows the beaded iron pigment apposition and indicates prior exposure to asbestos fibers in air. In addition, this particular person had pleural disease (see Figure 2). (Reduced from magnification ×400.)

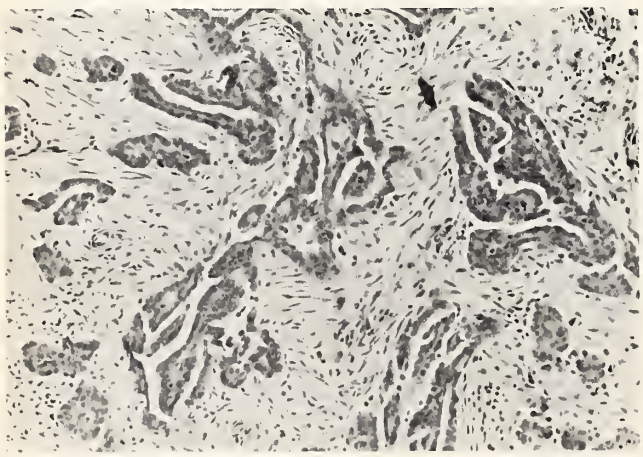

Figure 2.—Micrography of a biopsy specimen of the pleural mass from the person whose lung section is shown in Figure 1. The malignant cell growth shows a pattern resembling mesothelium. The cells form nests and sheets, overlying a loose fibrous stroma. This represents a mesothelioma, a disease that has been related to asbestos as an agent.[5,6] (Reduced from magnification ×100.)

Background

Definitions

We need to define many of the terms used to describe processes and disease findings related to growth, regeneration and neoplasia. This need arises from the use of descriptions of pathologic changes in a general and sometimes imprecise manner. Because the various responses seen in humans and animals may be only indirectly related to cancer, they should be clearly separated to define the relationships and processes involved in neoplastic disease. For these several reasons, an agreement on nomenclature is necessary.

Cell types from a replicating standpoint. The cells of higher organisms can be divided into two main groups, nonmitotic and mitotic.[7] Nonmitotic cells lose the capacity for division during growth and development, the adult form generally retains the defined gene product and they cannot be replaced if destroyed. Representatives of this population include central nervous system neurons and muscle cells. By way of contrast, mitotic cells retain the capacity to divide and hence can replace those lost. Two further categories of mitotic cells are seen in an adult organism: those that have stable populations, such as liver, and those with a labile population, such as the lining of the gut and skin. The former group of cells constitutes organs in which cell loss and replacement occurs, but the period between cell divisions is months to years; the mature cells and those that divide show little if any structural difference and no defined population of cells provides the new generation. In fact, the daughters of cell division resemble in large degree their progenitors.

Tissues with a labile cell population such as the epithelium of the gut and the skin usually have more rapid cell turnover with constant cell loss and replacement. Also, a defined germinal population of progenitors that frequently undergoes division is identifiable, providing cells that may further divide and differentiate. These differentiated cells after one or two mitoses frequently lose the capacity to divide, but further differentiation may take place.

Responses to physiologic demand. The response of these two tissue types to physiologic (or pathologic) demand is also different. Stimuli eliciting increased function produce divergent results. Nonmitotic cells can only increase their intracellular components, not the

number of cells. The resultant increase in tissue or organ size is designated *hypertrophy,* reflecting the increased size of its constituent cell population. Muscle hypertrophy with exercise is an example. Cessation of the stimulus results in increased intracellular catabolism with a return to "normal" cell size and hence organ size. Hypertrophy is a *reversible* increase in cell size resulting from an increased formation of specific and appropriate gene products. The phenotype of these cells does not change.

A similar stimulus to mitotic tissues increases the number of cells. This is termed *hyperplasia,* which occurs with maintenance of the appropriate phenotype. This also results in an increase in tissue or organ size. Of particular importance is that this response requires cell division; it is a *proliferative* response. The formation of calluses on the hands of a gardener is an example. The increased number of cells form in a normal manner and the daughter cells differentiate appropriately.

Not all hyperplasia is physiologic. Exposure of humans and rodents to dioxins results in a specific disease, designated chloracne in humans (Figure 3). These acneiform eruptions are comprised of hair follicles and sweat glands plugged with keratotic debris, the result of a hyperplastic response of the skin. Application of dioxin to mouse skin results in an identical hyperplasia (Figures 4 and 5). The dioxins in some manner cause the epithelium to increase in cell number, thereby increasing the formation of keratin that results in a plugging of the follicles. Cessation of the stimulus is associated with reversion to "normal," in this case because of increased cell loss while cell formation has returned to the "normal" rate. Of biologic importance is the observation that both hypertrophy and hyperplasia are *reversible* processes that maintain the "normal" phenotype and that hyperplasia, in addition, is a *proliferative*

Figure 3.—This worker's back shows a cutaneous disease with plugged follicles, chloracne. The man has had some 30 years of exposure to dioxins during employment at a chemical plant. No systemic disease has been identified. (This photograph provided through the courtesy of Dr Ray Suskind, University of Cincinnati.)

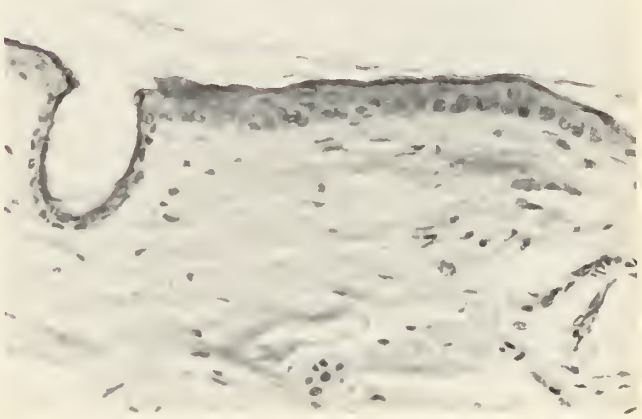

Figure 4.—Micrography of the normal structure of mouse skin. (Reduced from magnification ×250.) Note the thin multilayered epithelium and the hair shaft cut tangentially. The geometric appearance of the hair shaft may suggest a plugged follicle, but in reality it is not. Compare this micrograph with Figure 5.

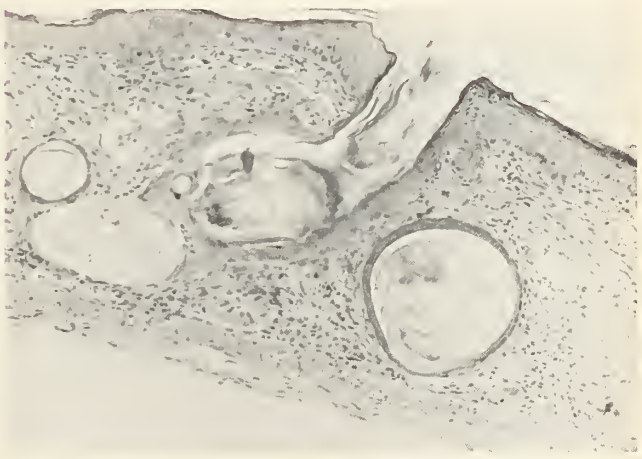

Figure 5.—Micrography of the skin of a mouse exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Notice the thickened and hypercellular epithelium. (Reduced from magnification about ×200.) In addition, the follicles could become plugged with the exuberant formation of keratinized material. This histologic pattern is identical to the one seen in humans exposed to the same material. (Mouse tissue kindly supplied by Dr Alan Poland, University of Wisconsin.)

process, one requiring cell division. Recall also that both processes can be responses to physiologic as well as pathologic stimuli.

Abnormal (pathologic) responses. Under abnormal circumstances the proliferative response may be associated with a change in the phenotype of daughter cells. Clearly, this change is restricted to cells capable of replication and involves further differentiation of the daughter cells so produced. This is best seen in epithelial tissue in which there is a defined germ pool from which the differentiating or differentiated cells spring (Figure 6). An example of this change is seen in bronchial epithelium in response to smoking. With exposure to this irritating gas, the daughter cells of the epithelium differentiate, not to tall columnar cells, but to a stratified squamous epithelium (Figure 7). These daughter cells replace the normal epithelium, initially lifting it and permitting the older, effete cells to be shed. This change in form, or *metaplasia,* is reversible. The differentiated cells, the squamous epithelium, do not revert to "normal." Rather, the change occurs in expression of the phenotype in the dividing cell population, permitting the newly formed "normal" cell population to displace the metaplastic one. With cessation of smoking, for example, the epithelial germinal pool resumes its normal phenotype with formation of an appropriate structure. For bronchial epithelium in humans, this restoration is believed to require five or more years.

The orderly development of epithelial structures requires both a proliferation of germinal cells and a timely and synchronous differentiation of the progeny. The cervical epithelium provides an excellent example in which parabasal cells divide and the resultant daughter cells are progressively forced lumenward. Concomitantly, the cells regularly express a change in

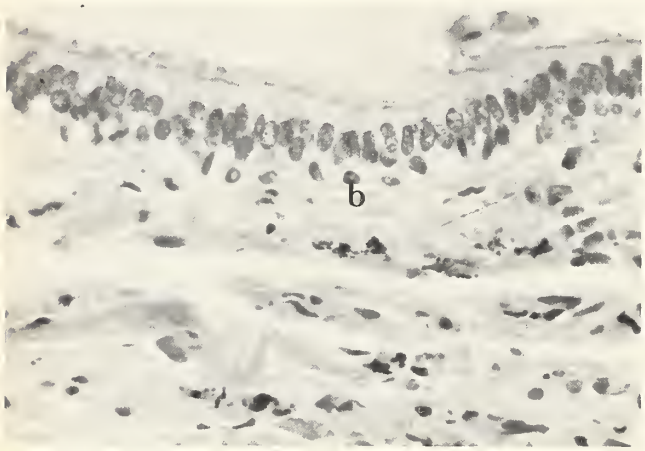

Figure 6.—Micrography of the respiratory epithelium of a nonsmoker. Note particularly the orderly array of tall columnar cells with cilia projecting into the air passage. Also notice the smaller basal cells **(b),** or reserve cells, lying along the basement membrane. These may be the germinal cells whose mitotic products form the tall columnar structures. (Reduced from magnification ×400.)

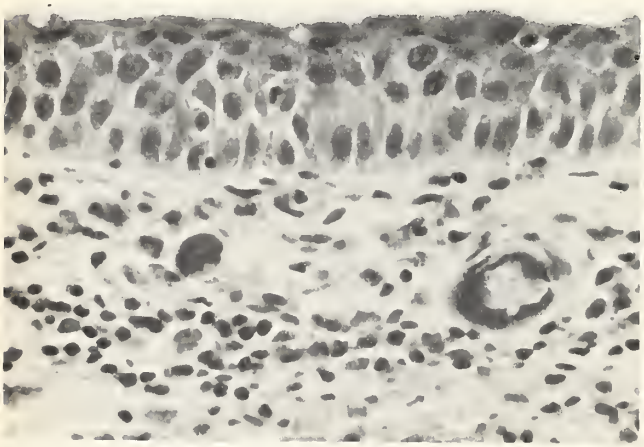

Figure 7.—This respiratory epithelium is derived from a smoker. The tall columnar epithelial cells are replaced by a stratified keratinizing structure. This is a *metaplastic* phenomenon, and one that is reversible. With cessation of smoking, the basal cells now forming this odd structure modify their direction of differentiation to replace the metaplastic lining with the tall columnar epithelial cells noted in Figure 6. (Reduced from magnification ×400.)

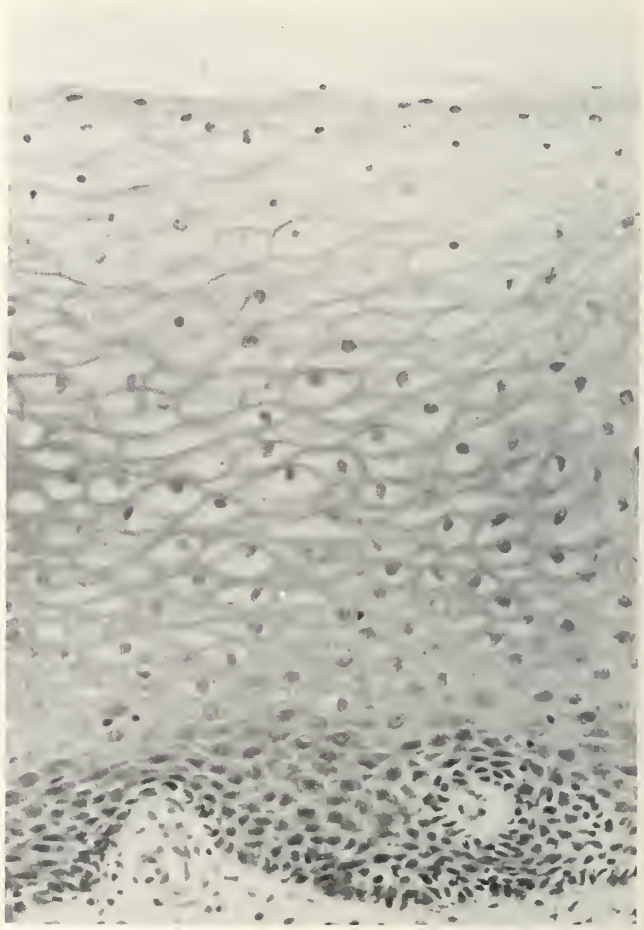

Figure 8.—Micrography of the cervix uteri of a woman at child-bearing age. Note the orderly progression from the basal cells to what appear ultimately as small keratinized structures at the surface epithelium. Particularly of note is a synchronous process of differentiation that is occurring, with first formation of glycogen-filled cells and then of the small squames. (Reduced from magnification ×250.)

phenotype; they become glycogen filled, proceed to show nuclear condensation and finally form flattened keratinized squames with small, shrunken nuclei (Figure 8). The mechanism(s) regulating this ordered synchronous development is not known. When this orderly and timely development is lost, a more chaotic, disordered and asynchronous growth occurs, called *dysplasia* (Figure 9).

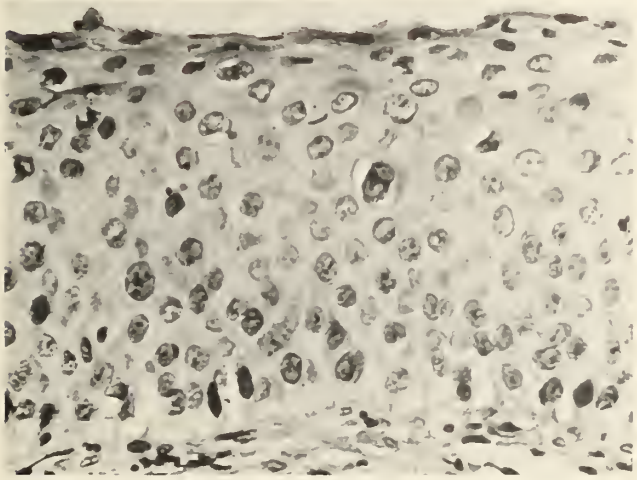

Figure 9.—Micrography taken through the cervix uteri of a woman to show the changes associated with dysplasia. Note that the differentiation to form glycogen-filled cells is lost, and the orderly progression from the basal layer to the flattened squames is not maintained. Premature condensation of the nuclei and the persistence of enlarged nuclei remain toward the surface. (Reduced from magnification ×250.)

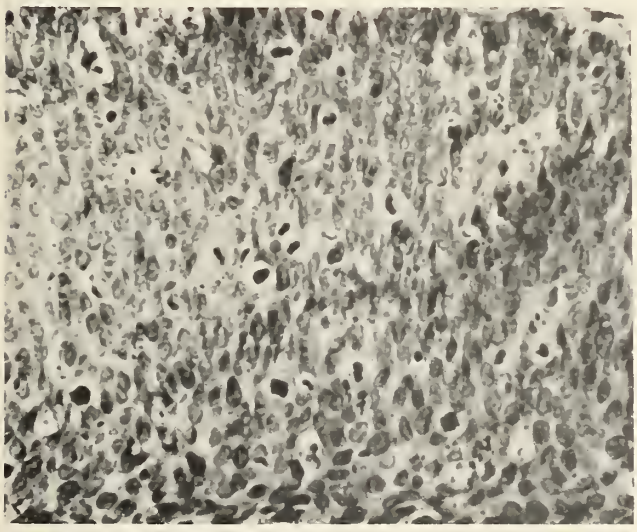

Figure 10.—Micrography taken from the cervix uteri of a woman showing the replacement of the normal epithelium by a disordered growth of cells that vary significantly in size, shape and staining reaction. Compared with Figure 9, a much more chaotic pattern is seen. This represents c*arcinoma in situ* of the epithelium. For reasons that are unclear, in this disease there is a period of time following the acquisition of this bizarre histologic (and apparently biologic) pattern and the actual process of invasion into the subjacent lamina propria. Our concept of disease suggests that the epithelium has all of the properties of malignancy but takes time to invade. In the cervix, this interval may be five or more years; for small cell carcinoma of the lung, the interval may be as short as the time for the second cell division.

In this malformation, the timing of differentiation is disturbed so that premature keratinization occurs deep within the epithelium, and cells without nuclear condensation are seen near the luminal surface. Furthermore, there are more mitotic figures than are seen in a reparative or hyperplastic process, and they occur more superficially. Finally, there is an increased number of aneuploid cells, suggesting a further distortion of growth.[8] Although controversial, there would appear to be dysplastic changes that are reversible and those that may become autonomous and hence result in neoplasms (see below).

In all of these previous instances, stimuli, defined or unknown, are required for the persistence of the change observed. Furthermore, with the exception of dysplasia, an orderly development in the expression of a recognized phenotype is noted. All of these changes involve cell proliferation.

Neoplasia. Teleology notwithstanding, the next step in this scheme involves the independence of the response from the stimulus. A *neoplasm* is defined as an abnormal tissue mass, the growth of which exceeds and is uncoordinated with that of normal tissue and it persists in the same excessive manner following the cessation of the stimulus that elicits this response. The process by which the cells of an organ or tissue acquire the characteristics of a neoplasm is designated transformation. The phenotype expressed by this new growth varies extraordinarily. The unique feature, however, is the continued replication of a cell population and the production of cells that retain the capacity to divide.[9]

There are two broad classifications of neoplasms. Benign neoplasms remain a localized overgrowth and force aside adjacent tissues, but do not penetrate tissue boundaries. In contrast, malignant neoplasms, or cancer, will invade and seed in different parts of the body

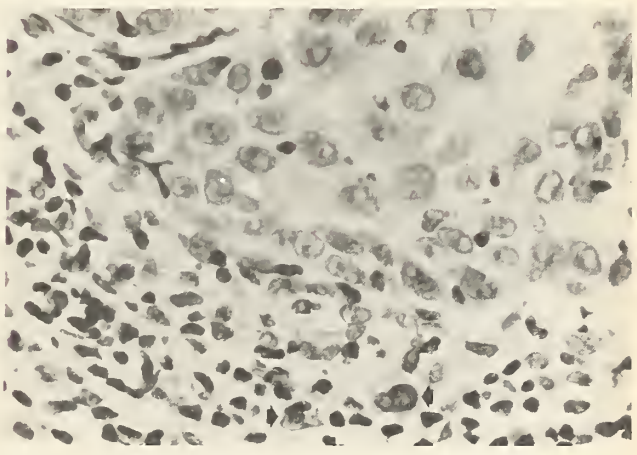

Figure 11.—Micrography of an example of early invasion. In this cervical epithelium there are several malignant cells **(arrows)** that have dropped away from the epithelium itself and have invaded the subjacent structure. It is this particular abnormality that is the sine qua non of malignant disease, here squamous cell carcinoma of the cervix. (Reduced from magnification ×400.)

(Figures 10 and 11). This invasion and distant seeding is a unique property; in this manner they kill the host. Although the sequence described has a variety of logical and, in fact, pathologic virtues, there are no findings that show that the pathway leading to cancer must traverse any or all of these several steps. The question whether or not benign and malignant lesions are necessarily related has been argued (see below). The neoplastic transformation appears to arise without any of the antecedent logical, but not necessarily required, steps of hyperplasia and dysplasia.[10]

Characteristics of neoplasms. A critical survey of the biologic nature of cancer has failed to find anything unique in the property of these cells with the exception of their capacity to kill the host.[11] This does not imply that cancer does not overproduce a product of a normal phenotype (for example, insulin production by a β-cell tumor of the pancreas) or of a normally suppressed one in an adult (for example, α-fetoprotein by hepatoma). The processes of invasion and metastasis are the basis for lethality, and, in fact, it is the latter process that more regularly kills a person.[12] Even these processes are not unique to cancer. The process of invasion is required for embryologic development. The secondary seeding of distant sites by blood-borne route is used, even in an adult human being, for the positioning of T and B lymphocytes and, in fact, many of the inflammatory cells. Neoplastic cells that are cancerous apparently express one or more components of phenotypes previously suppressed and at an inappropriate time in the course of a person's growth and development (for example, fetal antigens and constitutive enzymes). Especially important is the ability to continue to replicate and to invade. In fact, this observation that there are no "new" processes not previously expressed has led to the suggestion that cancer represents an aberrant form of differentiation[13-15] (Figure 12). Consistent with this notion is that most spontaneously occurring cancers arise in cell populations that are mitotic, and the most common ones are those that have a very active germinal pool (Table 1). The cancerous products of the transformation show "vignettes" of the cytologic features of the cell type.

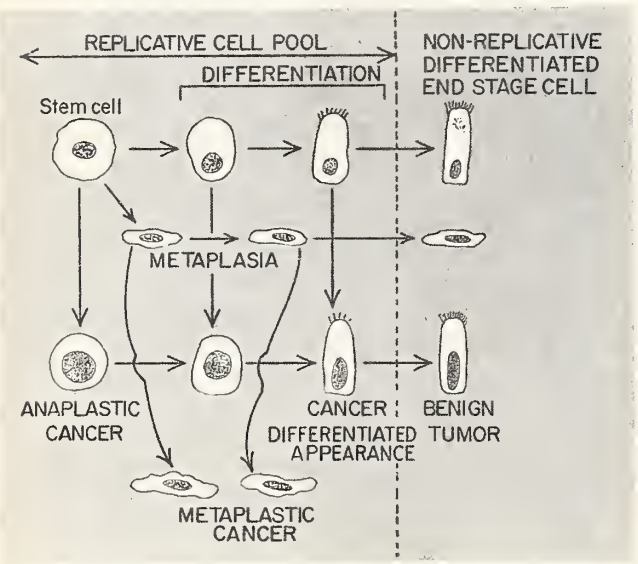

Figure 12.—A schema of the potential origins of neoplastic cells. Selection of one or more cells for transformation is assumed to occur from the differentiating pool. The differentiating cells may also have been subject to a metaplastic change. The new but inappropriate cell type can also be transformed to neoplasms. The resultant disease will then represent those structural and functional properties of the cell type that is selected. This provides a basis for the development of squamous cell carcinoma in the lung, for example. The acquisition of the ability to replicate by differentiated end-stage cell may be the basis for benign lesions (from Pierce et al[15]).

The frequency with which these terms are used indiscriminately or the processes are not defined provides some of the confusion that arises in understanding these diseases. Hyperplasia is confused with neoplasia (as, for example, warts with cancers in skin painting); transformation sometimes defines only growth properties. Additionally, properties of cancer cells are frequently confused with a host's response to a neoplasm (Table 2). Another background notion that has produced difficulty is the attempt to apply the approach that we have used successfully in analyzing microbiologically induced illnesses to the study of cancer.

Koch's Postulates Violated

Our technique for the analyses of the etiology of disease has arisen in large part from studies on microbiologically induced illness. This is a direct outgrowth

TABLE 1.—*Relationship Between the Potential for Cell Division and Organ Site of Cancer Development in Humans*

Nonmitotic Tissue	*Cancer Incidence*	*Mitotic*	*Cancer Incidence*
Neurons	Rare, usually childhood	Mammary duct	Common
		Skin	Common
Muscle	Rare	Bronchial epithelium	Common
Retinal rods	Rare	Pancreatic	
Adipose tissue ..	Rare	Acinar cell	Rare
		Duct cell	Common
		Liver	Common*
		Small bowel epithelial	Rare
		Colonic epithelium	Common

*Liver cell cancer is especially common in areas with high incidence of chronic hepatitis.

of the research efforts in the previous century and the beginning of this one. Robert Koch proposed that a specific agent causing a disease could be defined by identifying the microbial agent in the diseased tissues, isolating it from that tissue and then using that agent to induce the same disease in a similar or identical species. This sequence provided a logical and rational scientific ground for analyzing the pathogenesis of infectious disease processes, involving those produced by viruses. These principles are referred to as Koch's postulates. There are several features of carcinogenesis in general, and chemical carcinogenesis in particular, that point to the fact that Koch's postulates, as we understand them, cannot be so rigorously applied, especially in determining the cause of cancer.

The nature of neoplastic disease as we recognize it introduces a new set of responses not seen in infection. First, exposure to the agent used to induce a disease may have been temporally remote from the production of the cancer itself. A single exposure of an animal to a variety of chemical carcinogens may produce a neoplasm many months or even years remote from the initial single application. The agent itself may (and in fact must) be long gone when the neoplastic disease occurs. A single application of dimethylbenzanthracene to mouse skin can be "promoted" to have cancer develop two years later, when the cells initially exposed have been replaced. Second, the agent may not be identified within the tissue, either in its original form or as its metabolic product. Third, the agent itself cannot be isolated from tissue that becomes neoplastic. Fourth —an interesting outgrowth of this analogy—in microbial disease therapeutic regimens are directed toward the agent. In cancer our therapeutic regimens are directed toward the cells involved, not the causative agent (with the possible exception of interferon therapy or virally induced cancers). We may need to think in "non-

TABLE 2.—*Cancer Properties*

Intrinsic Properties of Cancer Cells	*Extrinsic Properties of Cancer (Host Mediated)*
Growth	Immunologic reaction to neoplastic cells
Invasion	Vascularization of tumor
Enzyme composition	Fibrosis (desmoplasia)
Surface markers (including antigens)	Site of distant spread (the fertile field)
Clonal selection for growth site (metastasis)	

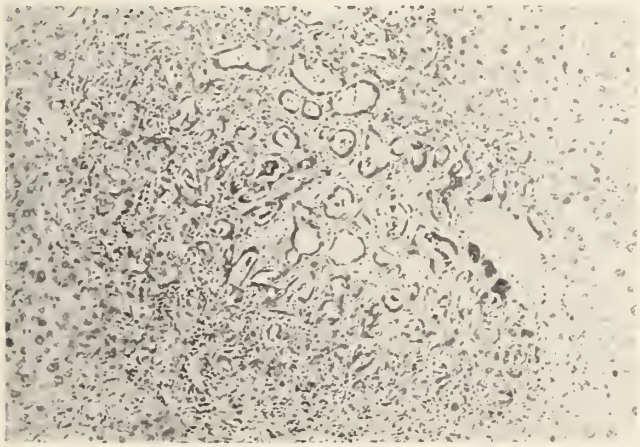

Figure 13.—Micrography showing the heterogeneity of cell types that are involved in the malignant transformation of a mouse liver following exposure to diethylnitrosamine. Specifically note the admixture of ductal cells, cells derived from the parenchyma and cells whose origin is less clear. The several different populations of cells all seem to show proliferation. Homogenization of this mixture for biochemical analysis gives an average of the diverse properties of all cell types.

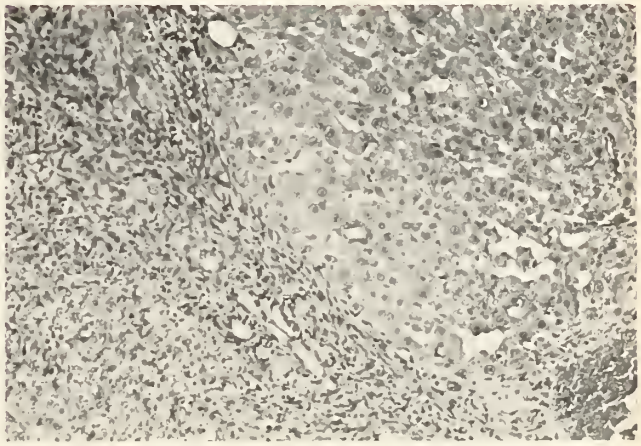

Figure 14.—Micrography of a portion of rat liver exposed to 3′-methyldimethylaminoazobenzene, showing several types of cell responses produced by this aromatic component. Notice in the lower half of the micrograph the variation in size, shape and staining reaction of this cell type and in the upper half a persistence of some order in the structure. In between there is a thin rim of tissue consisting of a peculiar admixture of cell types, perhaps including fibroblast. (Reduced from magnification ×200.)

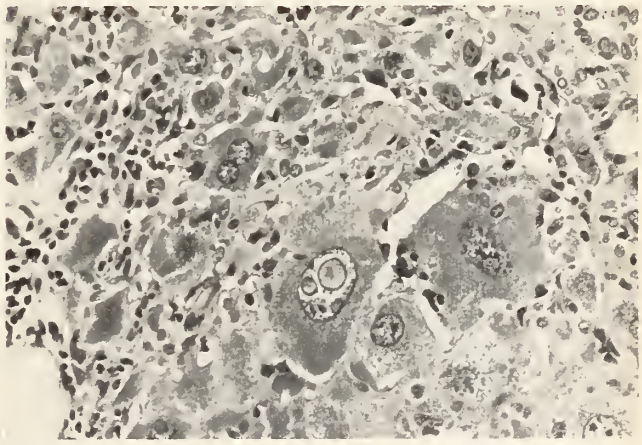

Figure 15.—Micrography showing the great variation in liver cell size, shape, number and staining reaction that appears in the midst of a neoplasm derived by feeding diethylnitrosamine to mice. The complexity of individual cell formation in a given neoplasm is clearly shown. (Reduced from magnification ×400.)

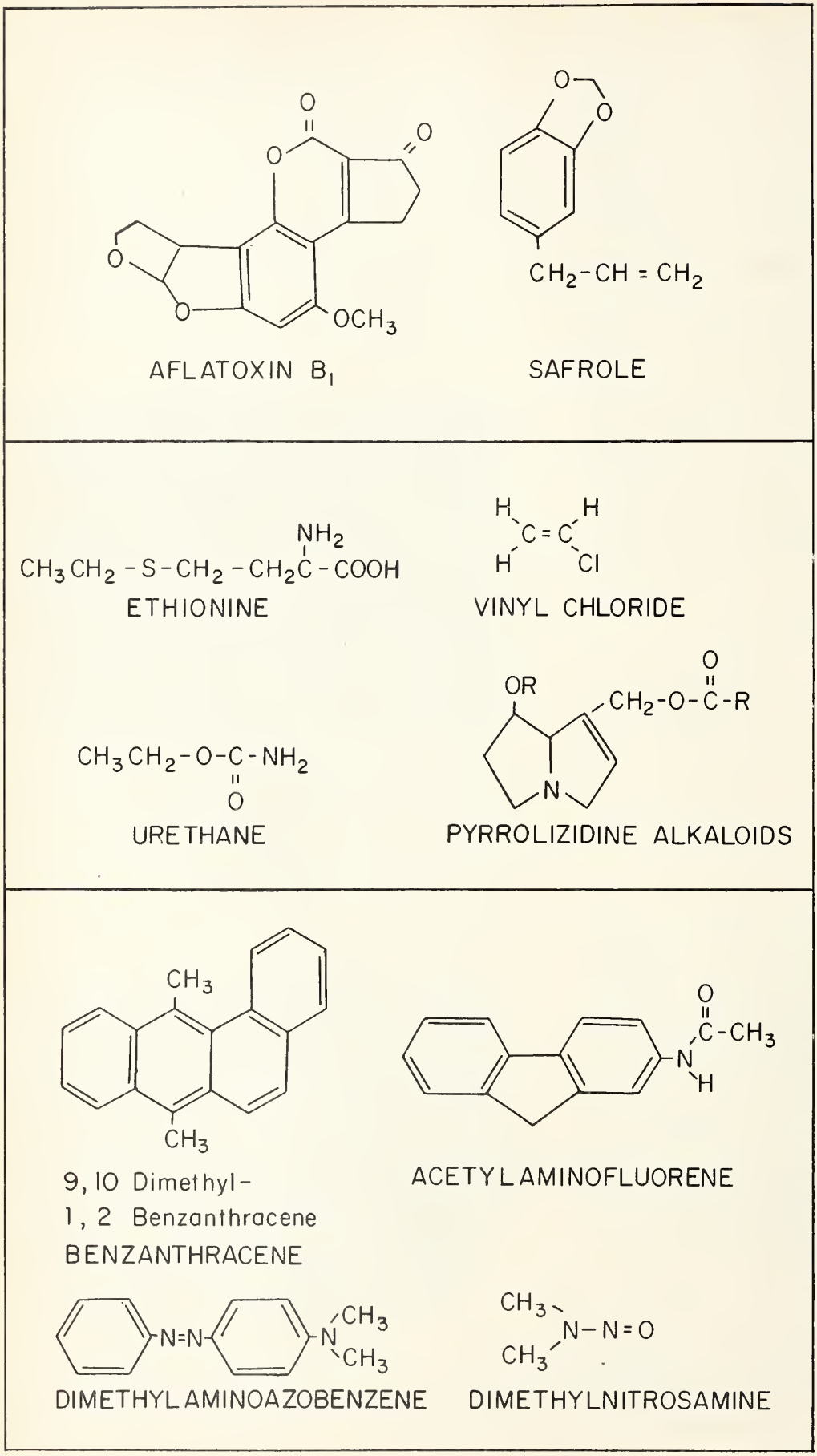

Figure 16.—These structural formulas show a variety of naturally occurring and man-made chemicals that have produced neoplasms in various eukaryotic species. Aflatoxin and safrole **(top)** are natural food products. Aflatoxin is derived from fungal contamination of a variety of foodstuffs and safrole is a product of the sassafras tree. Pyrrolizidine alkaloids **(middle)** are derived from specific herbal materials used in common "natural" health care and are found in a weed eaten by sheep in Australia that causes acute liver disease. These alkaloids are also agents producing veno-occlusive disease in drinkers of "bush teas." Vinyl chloride, ethionine, urethane **(middle)** dimethylnitrosamine, acetylaminofluorene, and dimethylaminoazobenzene **(bottom)** are derivatives of the chemical synthetic processes. Dimethylbenzanthracene comes from cigarette smoke and coal tar.

Kochian" terms to understand something about carcinogenesis, especially that produced by chemicals.

Historical Perspectives of Experimental Chemical Carcinogenesis

One of the first attempts to produce cancer in animals using chemicals involved the azo dyes. Injection of these materials beneath the skin of rabbit ears ultimately resulted in a typical epithelial proliferation at the site where the chemical was deposited.[16] There rapidly evolved from this initial observation a series of experiments that have both clarified and added further confusion to the problems of identifying the molecular biology of cancer production.[4,17,18] Most of the experimental systems involved the continuous exposure of an animal to the agent in question. Some time following the beginning of the exposure, proliferative and neoplastic diseases developed in one or more target organs. Most if not all chemicals that are carcinogens also cause cell death with replacement. Not only is there regeneration, there is also hyperplasia, phenotypic change and neoplasia (Figures 13, 14 and 15). This remarkable admixture of cell types and the variety of expression of a single cell type make a simple assay system clearly impossible. We need to further separate the host's response to these cells from changes in the cells as a group (Table 2). This is especially true in the liver. It also soon became apparent that the bewildering array of chemicals capable of producing cancer (Figure 16), the complexity of organ response and the variety of the chemical structure made any attempt to define a structural-functional relationship that causes cancer unlikely.[19-21] The simple addition of a methyl group, or its movement from one position to another on an aromatic ring, would render some agents noncarcinogenic (Figure 17). Replacing chemical groups of differing size and electronic configuration also changes the "carcinogenicity" of these chemicals. In other instances change of the target tissue susceptible to the carcinogenic agent occurred with manipulation of chemical structures.[22] Furthermore, simple dietary manipulation could also change the target organ.[23] It was then shown that many of these agents required metabolic activation.[24] This conversion of chemical species with lesser activity to more reactive forms is carried out by enzymes naturally present in many cell types, the xenobiotic or mixed-function oxidase system. This system is subject to dietary manipulation and to modification by the putative carcinogenic chemicals. Modulation of levels of these activating enzymes follows exposure to the carcinogen.[25] One of the metabolic products of the parent compound itself may be the biologically active compound that produced the neoplastic disease. Not surprisingly, some of the chemicals were rendered inactive on metabolic conversion, further confusing the issue. From these observations has grown the concept that there are "direct carcinogens" and "indirect carcinogens," some of which are converted to an electrophilic component, an ultimate or proximate carcinogen. This suggests that this agent may interact with some component of the cell. This chemical interaction was perceived as the means for causing cancer, a concept not dissimilar to the introduction of genetic information from oncogenic viruses to alter cellular behavior. In fact, macromolecular adduction has been pursued but no specific site identified that occurs for all agents (Figure 18). That binding occurred at times remote from cancer formation, that selective removal of the adduct occurred

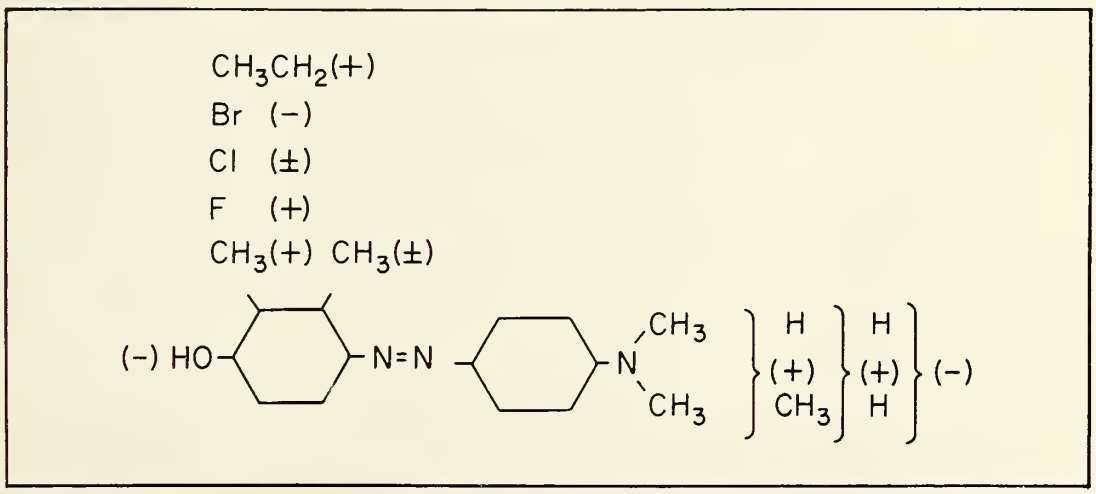

Figure 17.—This drawing shows the relative carcinogenicity of several derivatives of aminoazobenzene. For this substance to be carcinogenic, at least to rodents, there must be at least one methyl group substituted on the amine nitrogen. The elimination of both methyl groups results in a noncarcinogenic agent. The parent compound that has been used repeatedly is dimethylaminoazobenzene with a methyl substitution on the 3′ position on the second aromatic ring. The movement of the methyl group to the 2′ position, or the second position on the first aromatic ring, renders the material noncarcinogenic, or at least a weak carcinogen. Substitution at the 3′ position by an ethyl group rather than a methyl group, or by a fluorine atom, maintains carcinogenicity but substitution by a bromine or a chlorine renders the material noncarcinogenic. The positioning of a hydroxyl group at the fourth position also renders it noncarcinogenic.

and, in fact, further observation on the biology of this process made this simple explanation incomplete for elucidating the cause of cancer.

A complication to the mechanisms of carcinogenesis was identified by a series of experiments by Berenblum and Schubik.[27,28] They found that the production of cancer could be separated into (at least) two stages, one related to a carcinogenic agent called initiation, and the second related to the development of cancer from cell populations initiated by the carcinogen, termed promotion. It was shown that the initiation event was dose-dependent: more initiator applied resulted in more neoplastic disease. Surprisingly, the application of the initiator in small doses, not enough to produce cancer by itself, showed no structural or functional modification of the cells of the skin or of their progeny. Of course large quantities of the chemical could and do injure the skin. The effect of the initiator seems very long-lived despite the absence of structural and functional change. A single application of a carcinogen to the skin of a newborn mouse is associated with the development of an entirely normal mouse without defined cutaneous modification. Years later this same animal could be treated with a noncarcinogenic agent (the promoter), resulting in production of neoplasms of the skin (Figure 19). It follows that the initiator produces some type of heritable change in a subject cell population that many generations later, when exposed to an agent that produces cell replication, results in a variety of changes, including cancer. The agents are pure initiators; they will not produce cancer by themselves. Also, there are pure promoters, agents that by themselves only promote initiated cells. Although almost all promoters are mitogens, not all mitogens are promoters. The two-phased system has been extended from skin to lung, colon, liver and breast in experiments using rodents.[29,30] However, observations suggest that even the simple initiator-promoter sequence should be questioned.[31-33] Data have shown that initiators may follow promoters and still result in cancer.

Another confounding observation must also be considered. In rodent skin, the initial proliferative change is hyperplasia, a wartlike growth. To persist, these warts require the continued application of the promoter and are, by definition, not neoplasms. Some of these hyperplastic lesions do indeed become autonomous, no longer depending on an external stimulus for continued growth, and hence are neoplasms. Continued promotion of these benign lesions results in squamous cell carcinoma (Figure 20). These observations have been used to suggest that benign lesions are premalignant

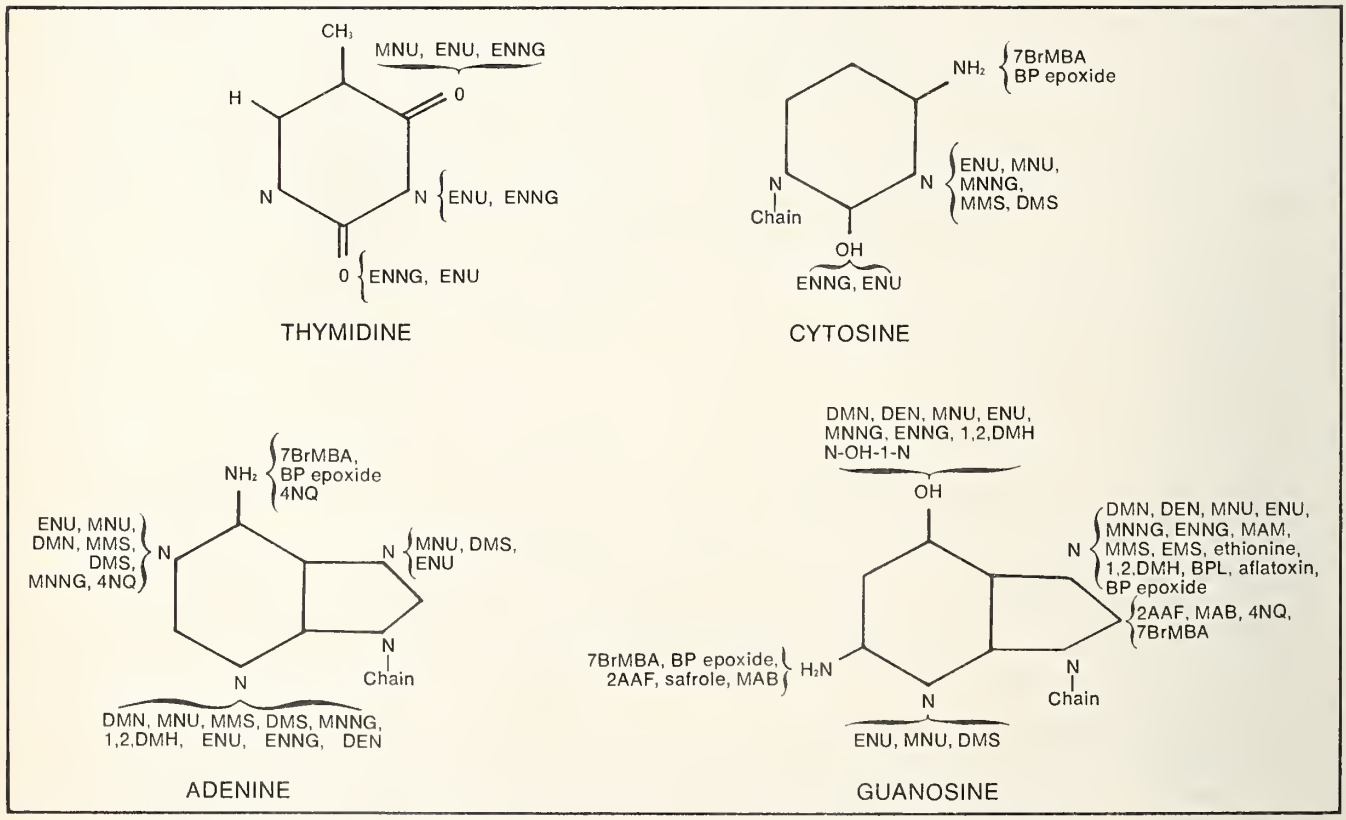

Figure 18.—This drawing shows the multiple and complex sites of interaction that occur with the nitrogen bases with diverse chemical carcinogens. Not only are many sites affected, but multiple sites are modified. MNU = *N*-methyl-*N*-nitrosourea; ENU = *N*-ethyl-*N*-nitrosourea; ENNG = *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine; 7 BrMBA = bromethyl-benzo(α)anthracene; BP epoxide = benzo(α)pyrene 7,8-dihydrodiol,0,10 epoxide; 4NQ = 4-nitroquinoline-*N*-oxide; DMS = dimethylsulfate; DMN = dimethylnitrosamine; MMS = methyl methanesulfonate; MNNG = *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine; 1,2,DMH = 1,2-dimethylhydrazine; DEN = diethylnitrosamine; N-OH-1-N = *N*-hydroxy-1-naphthylamine; 2AAF = 2-acetylaminofluorene; MAM = methylazoxymethanol; EMS = ethyl methanesulfonate; BPL = β-propiolactone, and MAB = 4-methylaminoazobenzene. (Modified from Farber.[26])

ones. The cancerous lesions that arise do not necessarily arise in the wart, or the benign papilloma; in fact, they may arise in the adjacent skin without a "benign" precursor. Similar observations have been made in rodent colon and small bowel carcinoma.[34] These findings suggest that the benign and the malignant lesions, though related, may be separate processes. Several questions arise immediately from this observation: first, which are the cells that become malignant and, second, how does the process of transformation, the third step in the neoplastic development, occur?

There is probably no more controversial area in chemical carcinogenic studies today than the identification of the cells that actually provide the origin of the malignant (in contrast to the benign) growth.[10] This has been extensively analyzed in breast, colon and liver. All of these studies have shown that there are multiple stages in neoplastic growth. The separation into initiation, promotion and transformation processes may not include all of the steps involved. Nonetheless, the multistep model provides the following information (see Figure 21). The initial interaction of the several different carcinogens occurs with a population of cells capable of replicating. This follows from the observation that nonreplicating cells would have been shed long before application of the promoter, at least in skin. Some modification of the genotype, not necessarily associated with altered phenotypic expression, takes place because the susceptibility to change is passed through several generations of cells before promotion. There are no defined modifications of skin, either structurally or functionally, before promotion. The promotional event causes increased replication of all of these cells. In fact, skin initiators by themselves produce "hyperplasia," though without focal areas forming warts.[35] From this replicating pool, an autonomous subpopulation seems to be selected that no longer needs the promoter to continue replicating. Within this last group there are two populations that seem to be selected, one with the capacity to invade and relocate to distant parts of the body, invasion being the unique property that makes them malignant. The second is a population of cells that, although replicating, remains local, forming benign neoplastic lesions. There may be a third group of cells. These form growths that remodel and even assume a normal structure.

The skin provides an interesting window through which changes in carcinogenesis can be observed. It is obviously readily accessible. A great deal of effort has been expended in understanding carcinogenic action in other organs, including liver, colon, breast and prostate. The liver was one of the first organs noted to be subject to transformation by chemical means and the organ in which metabolic conversions were identified early. Continued exposure of the liver to a carcinogenic agent results in a variety of remodeling steps, including the appearance of a hepatic fibrosis.[35] Within this modified liver structure, islands of cells develop, some of which apparently are autonomous; that is, removing the carcinogen from continuous feeding does

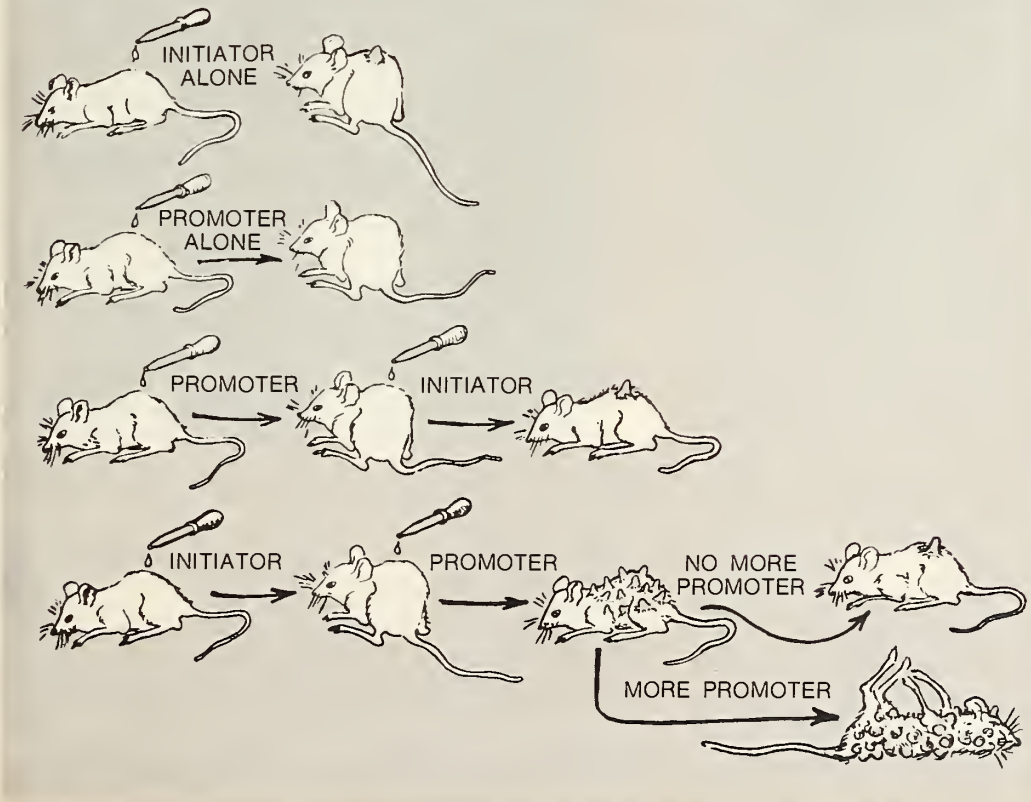

Figure 19.—This schema shows the results of the type of experiments carried out by Berenblum and Shubik.[27,28] The initiator alone on a single application might produce an occasional warty growth on the back of a mouse. Use of the promoter produced no defined reactive response. If the promoter was added before the initiator, the effect of the initiator itself was seen. On the other hand, if the initiator was followed by a promoter, a variety of growths occurred. Cessation of promotion resulted in the disappearance of many of these growths, but continued promotion ultimately led to the development of a true neoplastic disease that killed the animal.

not result in regression of the tumor. But there is evidence that many of these nodules undergo spontaneous remodeling and become "normal." Of special concern here is which cell populations are transformed because there are a variety of defined cell types in the liver. More recently two stages of carcinogenesis have been found in hepatic tissues as well as skin. The initial observation in this regard was made years ago by Velda Craddock, who found that the administration of an otherwise noncarcinogenic azo dye to newborn animals, when associated with a mitogenic stimulus—in this case partial hepatectomy—resulted in cancer.[36] More recently Peraino has used this system to show that materials such as phenobarbital can be used as an initiation-promotion event.[29]

The breast and colon in rodents have also been used in analyzing carcinogenic stimuli. In both tissues continuous exposure to a complete carcinogen results in the growth of a true neoplasm. In both, there is in addition the formation of neoplasia without malignant potential, which in all instances is preceded by hyperplasia that is reversible and requires the presence of the agent inducing the change.

In fact, this biologic aspect of neoplastic growth requires specific attention. It is this alteration of a subpopulation of cells that is particularly important in considering the final mechanism of carcinogenesis. Specific questions must be answered:

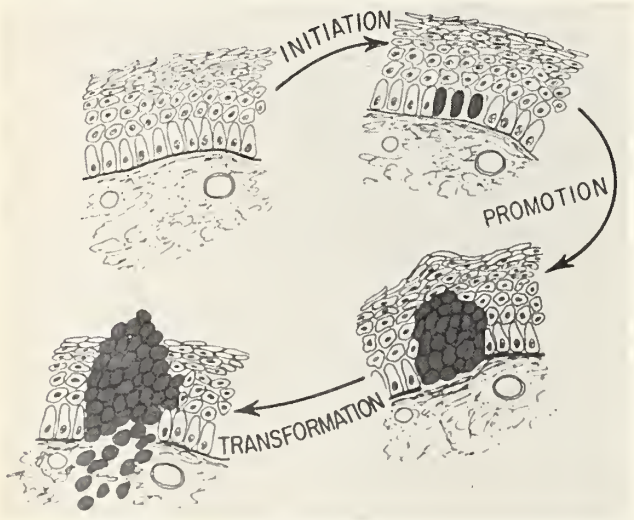

Figure 20.—A schema illustrating what is believed to represent the changes that occur in the initiation-promotion-transformation process. The application of initiator, a carcinogen, in some way modifies a group of cells capable of replication. These cells pass the modification and its information on to daughter cells, but without a structural alteration visible by microscopy or detected by functional means. Later the addition of a promoter, many of which are mitogens, causes these cells to proliferate. This resultant warty growth, with continued promotion, may be the site of transformation with the appearance of an autonomous neoplastic cell population. These cells penetrate into and invade subjacent tissue. It should be pointed out that the point of transformation may not necessarily be at the site of the warty growth, but can occur in adjacent, supposedly unmodified, skin.

- Is a single cell or small population of cells (monoclonality), or a multiple population of cells (polyclonality, field effect) transformed? As yet there is no answer to these questions.[37] Attempts have been made to determine the clonality of human and rodent cancers, and divergent results have been obtained. Many chemical carcinogens in animals that affect the hematopoietic system result in monoclonal growths. Human cancer of the hematopoietic system also appears to be monoclonal. Solid neoplasms, on the other hand, and epithelial neoplasms particularly seem to be of mixed populations, yet a common human benign lesion—leiomyoma of the uterus—seems to be monoclonal. A problem with these analyses is that they do not test for the initial outgrowth. The selective pressures of both population growth and clonal selection may artificially induce monoclonality or polyclonality. Recent analysis of the mechanisms of metastasis have clearly pointed to a heterogeneity in malignant cell populations and, additionally, an instability of phenotype (or genotype? see below).[38,39] This and the selective growth success of specific clones provide an explanation for "progression." This latter term refers to the acquisition of progres-

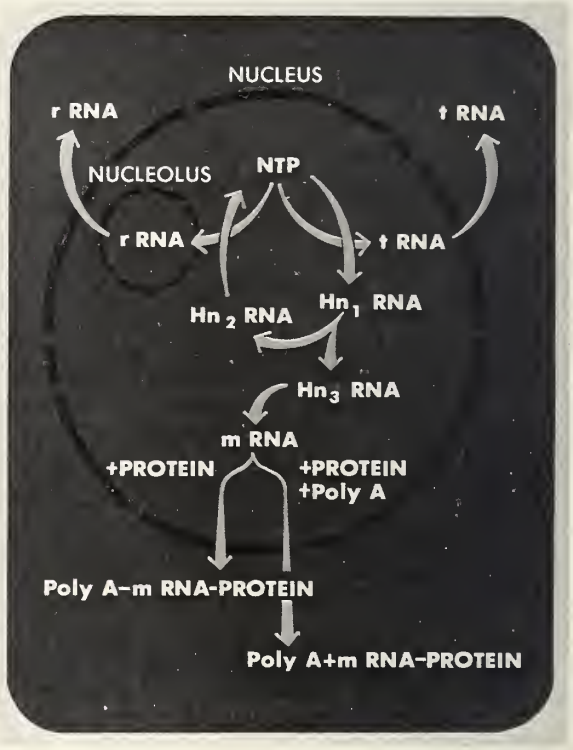

Figure 21.—This cartoon depicts the several processes of ribonucleic acid (RNA) formation, modification and release. RNA transcripts are formed from a nucleotide precursor pool (NTP). The several polynucleotide macromolecules formed must then be processed (for example, transfer RNA [tRNA] is transcribed in a size larger than the final product; the transcript must be reduced in size before release). Some of these RNA polynucleotides are lysed in the nucleus and their bases are returned to the RNA pool; others are further metabolized. Messenger species (mRNA) are edited, capped and polyadenylated before release from the nucleus. Not shown are small nuclear RNAs. rRNA = ribosomal RNA; polyA = polyadenylic acid, and Hn_1, Hn_2 and Hn_3 RNAs = heterogeneous nuclear RNAs.

sively more "malignant" and autonomous behavior by cancer with continued survival.

- We also do not know whether a single cell or a single group of cells or multiple populations of cells are transformed to form cancer.[40,41] The experimental models point to the fact that multiple sites can become malignant and not necessarily in a concordant temporal manner. This implies that the biologic examination of the process is necessarily going to be difficult.

- What is the cell of origin of a malignant disease? Cells that do not replicate cannot be cancerous; by definition neoplasms are autonomous, proliferating lesions. It follows that end-stage cells that have sacrificed the capacity to divide are not progenitors of neoplastic growth. A reflection of the site incidence of this disease in adult humans suggests the truth of this observation, that those cells that are stable and nonmitotic rarely produce cancer (Table 1).

These observations and the findings on skin carcinogenesis suggest that it is the germinal pool that is subject to the effect of carcinogens, and that this capacity for cell division renders the genetic information in some way susceptible to further change. In vitro assays for chemical carcinogens confirm that at least one round of cellular division is necessary to produce a neoplasm. In stable organs such as the liver, wherein a variety of cells may be called on to divide, identifying the subject population is much more difficult. This may explain the variety of nodules that appear in stimulated liver cells. What does seem apparent, however, is the fact that in the induced cancers, the cells of origin, or replicating pool, are from a pool of cells that can be recruited for replication. This is important in considering the contrast in behavior of these several populations. This point will be discussed later.

- Are there unique properties that are expressed in benign and malignant tumors? By definition, benign tumors are autonomous replicating pools of cells that force aside adjacent tissues. Their histologic pattern and their biologic characteristics show no unique features that do not occur in normal tissue, at least some time during development. They may show varying degrees of differentiation and concomitantly a variation in pattern of their biochemical markers. Consider again for a moment the skin model. These neoplasms arise from germinal cells, and the process of transformation only renders them capable of continued proliferation. The benign lesions resemble basal cells, both structurally and functionally. Similar observations must be made about malignant tissue. These cells, too, show a variation in cell pattern resembling the tissue of origin, but the most notable feature in the adult organism is the propensity for invasion and distant spread. The process of invasion is a normal component of almost all embryologic tissue. The distant spread, blood-borne metastasis, is a necessary component of avian embryogenesis and the biology of lymphocytes in the adult population (see above). These growths apparently have no unique biologic features, only that the time of appearance of these otherwise suppressed phenotypes is abnormal and the end result produces a hostile cell population. It follows that finding a unique tumor marker is unlikely because these tissues or organs will represent no more than what has been present during the ontologic development of the tissue or organ. There may be changes in quantity, but changes occur necessarily in quality. A search for unique markers, constitutive enzymes and neoantigens has most frequently shown similar entities in the germinal pool or developing tissues. Even the "abnormal" glycoproteins on the cell surface reflect the structures in immature cells.[42]

There is a further property of neoplastic growth that deserves iteration. Endocrine-dependent cancer frequently becomes less dependent on hormonal stimulation for continued growth. Also, during the course of cancer, the tempo of growth will frequently increase, accelerating the death of the host. This change in the biology of cancer has been referred to as progression. Recent studies have shown that early cancers are a heterogeneous mixture of phenotypes.[12] The progression observed suggests a natural selection of one or more cell types over others because of more favorable growth properties. Additionally, a "genetic instability" may occur in the neoplastic population, consistent with the aneuploidy of tumor cells. These latter observations are not necessarily typical of karyotypes of cancer, but they do point to either a selection of some genotypes or a heterogeneity and instability of genotypes. Perhaps it is important to recall these features when considering the hypotheses for chemical carcinogenesis.

Mechanisms of Chemical Carcinogenesis

Our increased understanding of biology has made more difficult a simple explanation for growth, development and differentiation. Elegant and interwoven control mechanisms have been identified that regulate gene expression, but the regulatory phenomena for controlling cell division and specific forms of differentiation are not yet at hand. This is clearly relevant to the proliferative nature of cancer. The data reviewed above support the notion that benign growth (that shows continued replication) and malignant growth (that also shows invasion) additionally show altered forms of differentiation. In both instances the selection of a genetic expression reflects the ontogeny of the cell type. It does not indicate why there is the modification of phenotype, or if the modification of phenotype is cause or effect. Early suggestions for the basis of chemical carcinogenesis involved an acquired or spontaneous mutational event. Another more recent suggestion involves an alteration of epigenetic regulation. Perhaps a combination of these and other events leads to cancer. It is beyond the scope of this review to consider radiation, solid state and viral carcinogenesis.

The Mutational Theory of Cancer

The initial observation that carcinogens were metabolized to active electrophilic agents and that these agents would interact with specific areas in DNA provided a useful hypothesis for the acquisition of a malignant phenotype—an induced mutational event had occurred.

The mutation was related to adduction to DNA by the ultimate carcinogen. Undoubtedly this was and is an important observation. As a complete explanation for the disease, several problems remain. Multiple and diverse sites of carcinogen DNA interaction occur (Figure 18). Our current concepts of gene action point to these multiple and significant mutational changes as "sledgehammer" events. Also, Magee, Hultin and Farber[43,44] initially showed that the degree of modification of macromolecules does not correlate with the target sites for the ultimate development of malignancy. Furthermore, these modifications can follow the initial and perhaps single application of the carcinogen, and unless this modification is heritable, it becomes difficult to relate it on a one-to-one basis with the origin of cancer. The studies of macromolecular binding use a variety of cells on any organ for the source of the material. We now recognize that not only are the altered macromolecules derived from cells modified by the carcinogen, but an additional contribution can be derived from cells that are not modified (Figures 13, 14 and 15). The use of mixed-cell populations and cell populations already programmed for replication (for example, 3T3 and 3T10-1/2 cells) creates further complications. These considerations are counter to the hypothesis of a simple relationship between polynucleotide change and altered growth properties.

In recent years considerable extrapolating of the analyses of the macromolecular binding to cellular constituents has been done. It has been shown that the metabolic products of activation may indeed interact with these cell components, both DNA and RNA, proteins and glycoproteins. Even DNA precursor modification has been identified.[45] Incorporating the modified bases into DNA might result in significant modification of the genetic code. Even the fidelity of DNA transcription has been called into question in carcinogenesis.[46] Attempts to determine if one or more of these modifications are long lasting have been undertaken, but no specific reproducible adduction has been found. For this reason, it is also suggested that perhaps the mutational event, adduction to DNA, can be rectified. Support for this notion is derived from the fact that persons with xeroderma pigmentosum, a repair-deficient syndrome, succumb to cancer if exposed to ultraviolet light.[47] It is observed that chemical adducts can be excised effectively, even by specific enzymes already in the cells. Possibly a spontaneous mutational event occurs during the repair process in the cellular constituents, resulting in this neoplastic mutation.

The mechanism envisioned is an alteration of the genetic code, selecting for a population of cells that have the unique capacity for continued replication. Some support for the notion of a specific genetic defect has arisen from studies of human cancers, wherein specific genetic modifications are identified by karyotype analysis.[48-50] Even within the small population of cells that are readily subject to this type of analysis, an inconsistency in karyotypic change can be found.

One piece of information from these studies has direct relevance. Human chromosomes 5, 7, 8, 9, 11, 15, 17 and 22 are most frequently affected. In fact, it has been suggested that the human oncogenes c-*mos* and c-*myc* are located on the long arm of chromosome 8 at Q22 and Q24. It is also suggested that a translocation placing this segment downstream from a promoter region will activate this replicative mechanism. Support for this concept comes from studies of immunoglobulin synthesis of neoplasms. Karyotypic assays show a juxtaposition of the oncogene with DNA coding for the globin formation. This repositioning results in an immunoglobulin-secreting neoplasm being produced.[49,50] Considering all this, a potential modification of genetic information may be necessary, but perhaps not enough for the development of an autonomous neoplastic growth.

Support for the concept of a genetic change as a partial but not a complete explanation of transformation came from the analysis introduced by Ames and Hooper in which a correlation was made of mutational events found in bacterial species with the ability of specific chemicals to produce cancer in animals.[51] The initial enthusiasm for the correlative nature of this assay has been tempered with time, and now it is thought that the concordance of agents known to produce neoplastic disease in eukaryotypes and those that are mutational is certainly not one-to-one.[52] Admittedly, the problems of activation in a specific cell population as targets may be different and would therefore render this assay less "clean." An additional problem currently being addressed is the "potency" of the carcinogens; that is, the amount of exposure necessary to relate the agent to the production of disease.

Evidence derived from molecular biology now suggests two other areas that require further analysis. The identification of large quantities of reiterated genetic information has posed a regulatory role for these species as promoter regions in DNA, that is, polynucleotide sequences that act as switches to direct transcription of specific genetic material.[53-59]

Furthermore, at least some of these groups can potentially be relocated during mitosis in the genome, also suggesting such a role. The erroneous placement of such a regulator "upstream" from a gene sequence coding for replication would render the resultant cell population capable of beginning a neoplastic process, dividing, as noted, for chromosomal translocation.[49] A chemical can modify the code by changing a base to initiate such activity. The identification of a left-hand DNA helix, the Z form, adds another potential regulatory mechanism. Adduction to potentially modify the DNA helix to a Z form has been suggested, and could also participate in such a change.[60] Last but not least is the identification of DNA-associated protein adduction with a similar potential for control modulation.

The finding of genetic information in cells homologous to retrovirus genes, as the *sarc* and *myc* groups, further supports the existence of an endogenous coding region that might be activated by either alteration of a promoter region or relocation in the DNA se-

quence.[49,61,62] In fact, the chance placement of the avian leukosis virus "downstream" from a cellular "oncogene" not only may occur, but could explain the inefficiency of this virus species in contrast to others to control the expression of their "own" oncogene.[62]

Recently the mechanisms of activation of the human oncogene have been sought in bladder carcinoma cells.[63] A base pair modification was found, not in the promoter region but in the gene itself.[64,65] This then requires careful reanalysis of the potential for a point mutation to activate an oncogene, but does not explain the apparent need for a round of replication, at least in eukaryocytes, to "fix" chemicals for carcinogenesis. Furthermore, this does not explain the diverse properties of cancer cells.[66]

Altered Epigenetic Regulation

The concept of epigenetic regulation (and its potential dysfunction in cancer) lacks a specific biochemical explanation. Obviously no significant "mutational" event occurs during differentiation, either during embryogenesis, organ formation or in an adult.[15] Observations suggest that deletion of genetic information may take place during development, and that relocation of "transposable" elements occurs. Furthermore, methylation and acetylation of DNA and its associated proteins have been implicated in the regulatory process, even in viral infection.[67-71] Metaplasia is associated with the appearance of tissue with a different phenotype. This change is reversible. With cessation of the stimulus, the proper mode of differentiation is restored and the cells generating the tissue respond by reforming normal structures. This suggests retention of the appropriate gene sequences, and this phenotype can later be reexpressed. Furthermore, the ability to implant a malignant teratocarcinoma cell in a blastocyst of a mouse, which then develops into an ostensibly chimeric mouse, formed of normal and teratocarcinoma-derived cells capable of further reproduction, suggests there are external means of modifying the malignant phenotype.[72-76] Finally, results of the fusion experiments by Ephrussi and Harris also suggest that the malignant phenotype may not be the dominant expression in malignant cells.[77-79] These all point to the fact that differentiation is a regulated process, that the malignant phenotype is subject to regulation and that differentiation gone awry may underscore the changes seen in cancer.[15]

This phenomenon has been shown by recent developments in molecular biology to be more complex. First, the immutability of the genetic code has been called into question with the identification of transposable elements.[53-56] The relocation of specific genetic sequences suggests that modification of the code may be associated with development and with a change in the phenotype. Although this does not fit with one concept of a classic mutation, it does provide a change in sequences, perhaps in activity, and hence in phenotype. Also, data suggest that genetic information is deleted during growth and development, selecting for specific phenotypes with the potential loss of segments that are not required. Third, the identification of an oncogene, or transforming gene, in normal cells has added another dimension to these analyses.[80,81] This transforming gene provides a cell population with the capacity to replicate, a characteristic of malignant growth. The appearance of specific gene products from this genetic sequence in cancer in humans may also direct attention to the epigenetic system. Regulation of continued growth and a potential acquisition of more primitive phenotypes that occur could be modified by epigenetic processes if the information is always present but expressed at only specific times (see above). Finally, the knowledge of a repair mechanism that protects the cells of a recipient population from the effect of external circumstance adds another dimension to our capacity to withstand our hostile environment.[82]

Perhaps it should be noted in passing that the understanding of viral carcinogenesis, although somewhat

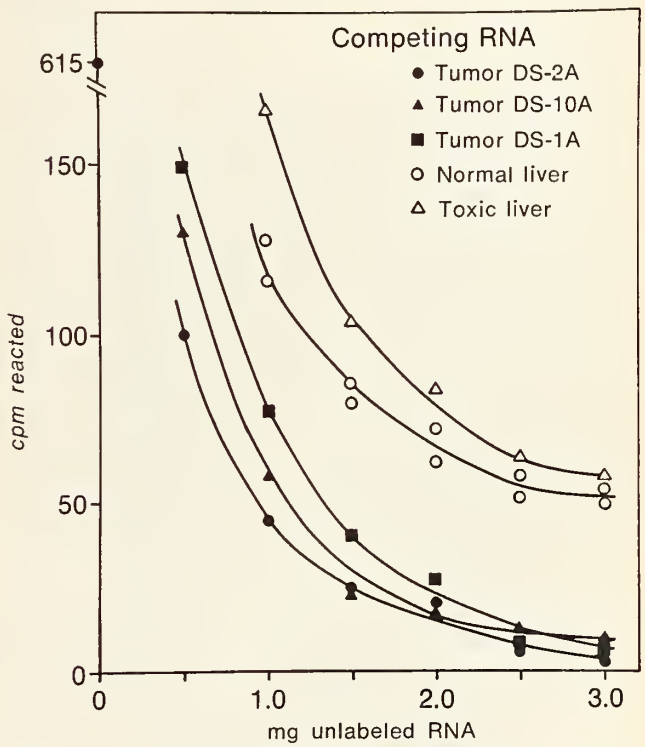

Figure 22.—This graph shows competition hybridization studies done to show that there was a release from the nucleus of nuclear-restricted RNA into the cytoplasm in livers transformed by chemical carcinogens, but not in normal liver, nor those animal livers exposed to equimolar concentrations of a noncarcinogenic analog. Liver DNA was fixed to nitrocellulose filters. RNA derived from the nucleus was labeled and allowed to hybridize with the DNA. Competing RNA derived from the cytoplasm of azo dye-induced hepatomata (DS-2A, DS-10A, DS-1A), or from normal liver or noncarcinogen analog liver were competed against the labeled cytoplasmic RNA in increasing concentrations. The curves for normal or toxic liver cytoplasmic RNA reached a plateau showing that there were sequences in the nuclear RNA that were not in these cytoplasmic macromolecules. On the other hand, cytoplasmic RNA from the tumors did compete completely, suggesting an identity of sequences. This was interpreted to show the release of these nuclear-restricted RNAs to the cytoplasm of cancer cells. (Reproduced with permission from Shearer and Smuckler.[95])

less confusing, still does not answer the basic questions concerning the development and acquisition of malignant phenotypes. The presence of new genetic information—that is, the selection of cells that will continue to replicate and invade—still requires an explanation of where the resurrection of information for primitive behavior may be in this cell population.

Epigenetic regulatory mechanisms operate at the levels of transcription and modification of a transcribed product. By definition they act on or regulate transcription, by modifying either the availability of DNA or of the transcribing mechanisms. The presence of methylating and acetylating activities has been implicated in the selection of gene sequence expression, even in humans. In the latter instance, selective modulation by pharmaceutical means has been used to reduce methylation and thereby reduce formation of a specific gene product[71]; this has been used to reexpress suppressed information. The modulation of levels and activities of RNA polymerases has been described.[83] The product(s) of transcription, the several RNAs, is another area to consider.

There is gathering evidence that RNA formation and metabolism within a nucleus are far more complex than those that occur in prokaryotes. Specifically, Harris showed a remarkable intranuclear turnover of newly formed RNAs.[84,85] Shearer and McCarthy showed that a selection of subsets of these RNAs appeared in the cytoplasm[86] and, more recently, both the polyadenylation of some of these RNA species, particularly those with messenger-like activity,[87,88] and a capping of the RNAs have been described.[89] Busch and co-workers have identified a variety of small RNA species with chemical similarities to messenger-like components that may also play a role in these interactions.[90] This is shown in part in Figure 21 in which is diagrammed the formation of several different RNA species in a nucleus, including transfer RNA (tRNA) and ribosomal RNA (rRNA). Additionally, heterogeneous nuclear RNAs of several different species occur. The turnover with lysis and return of the components is shown. The products of turnover of these RNA species are returned to the nucleotide pool. Some of the heterogeneous RNA is processed, including splicing and shrinking, to form messenger-like species. These messenger-like RNAs are released to the cytoplasm following polyadenylation and a capping of the 3′ end-specific systems. Last but not least, the entire process of release from the nucleus to the cytoplasm is a particularly selective one, and one that is energy-dependent, at least in vitro. This will be further discussed below. The possible role of the small nuclear RNAs in the splicing process has been mentioned and provides another regulatory mechanism. The significance of these several interactions is currently under critical review, germane to which is the relevance of these epigenetic systems to altered regulation in carcinogenesis.

What is the evidence for an epigenetic modification in cancer? The most compelling evidence is that the malignant teratocarcinoma cells can be made to act as a normal cell population and even differentiate into specific organs when placed in an appropriate environment.[72-75] Furthermore, the hybridization experiments of Ephrussi, Harris and others[77-79] point very carefully to the fact that there seems to be diffusible material present in cells that modifies the malignant phenotype. The identification of specific binding proteins in the cell cytoplasm[91] and of several nuclear RNAs that vary in transformed cells and the potential back-diffusion of proteins and RNA into the nucleus point to a regulatory step.[92] Finally, information suggests that there is no readily identifiable change in gene sequence expression in malignant cells, specifically in the liver.[93] The regulation and handling of these gene sequences are modi-

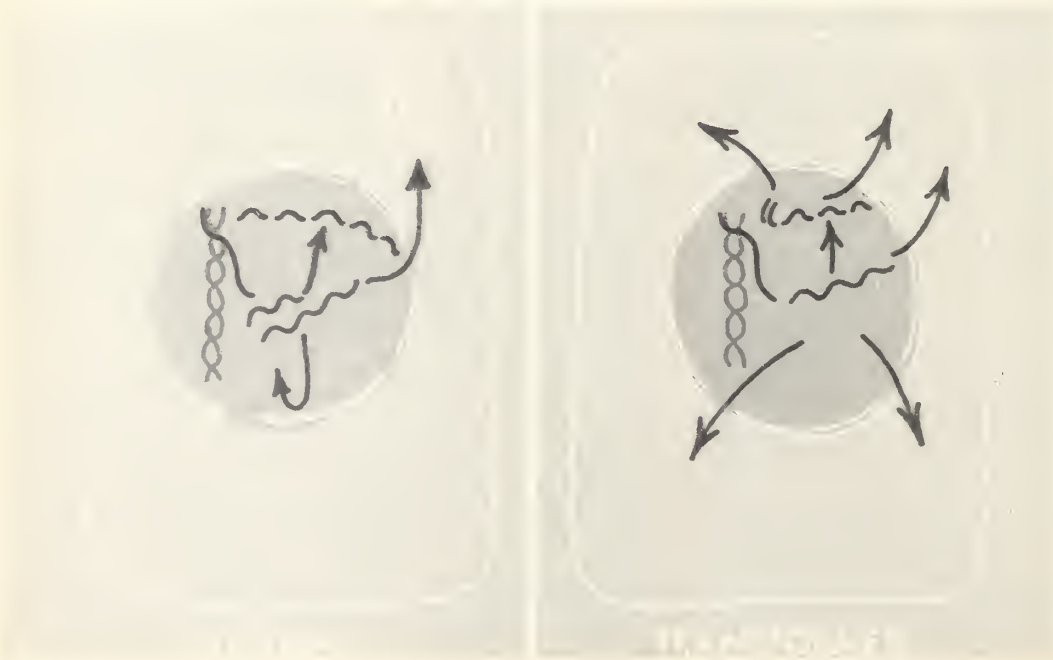

Figure 23.—This schema shows the modification that occurs in the transformed cells. Whereas in a normal cell there is an intranuclear process of synthesis and turnover of RNA with a selective release of specific sequences to the cell saps, in a transformed cell there seems to be a leak of many and diverse RNA species out of the nucleus. rRNA = ribosomal RNA, mRNA = messenger RNA, tRNA = transfer RNA.

fied.[94-97] To determine the status of nucleocytoplasmic transport of RNA and its stringency in transformed liver cells, analyses of the cytoplasmic RNA are undertaken by competitive hybridization. Gene sequences normally restricted to the nucleus (heterogeneous nuclear row) appear in the cytoplasm of transformed cells (Figures 22 and 23). Qualitative and quantitative differences were found in developing and regenerating livers. Additional studies have shown that not only reiterated sequences (detected by competitive hybridization), but messenger-like RNAs and single-copy RNAs are "leaked" to the cytoplasm. Furthermore, this occurs in transformed human cells and follows only carcinogen exposure in rats. In point of fact, modification of the transport phenomena has been identified in cells exposed to carcinogens[98] and in malignant cell populations.

If nothing else, this can provide a heuristic explanation of the appearance in malignant tissue of previously sequestered or suppressed genetic information. This includes constitutive enzymes and "neoantigens," or fetal antigens. This has been nicely shown in the case of α-fetoprotein and the appearance of the transformed state in liver.[99]

The problems of identifying the mechanisms of RNA transport from the cytoplasm to the nucleus are currently under investigation. An in vitro model has been devised to analyze this phenomenon. Briefly, animal nuclei are prelabeled with an RNA precursor such as orotic acid and then isolated from the organ, usually—but not invariably—liver. The isolated, separated nuclei are then suspended in a sucrose-containing buffered medium and incubated in vitro. In the absence of an energy source (for example, adenosine triphosphate), little if any RNA is released, and that which does transport is tRNA. The addition of adenosine triphosphate is associated with a remarkable enhancement of the release of both messenger-like species and smaller granules of transfer and ribosomal RNA.[100] This is schematically shown in Figure 24. It was found that the nuclei isolated from animals exposed to carcinogens and from chemically transformed cells released more RNA, frequently without the energy dependence of normal nuclei.[102,104] This suggested a modification in the regulation of this particular restriction mechanism. A high degree of correlation of the release of RNA and an adenosine triphosphate-lysing enzyme within the structure of the nucleus has been shown. Furthermore, exposure to carcinogens results in significant increases in this adenosine triphosphate-lysing structure and concomitantly RNA leak.[97] The persistence of the change long after the exposure to the carcinogen and the difference in this response in animals exposed to noncarcinogens suggest that this modification of cell function is an early response to the effect of carcinogens on liver.[105] This may represent an initiation step, a change necessary but not enough, for transformation by itself. Taken as a whole, these data clearly show that another form of regulation in addition to genetic coding, processing and splicing of the RNA may be modified in injury and specifically in transformation.

Summary

It is possible to summarize these several and many proposals for mechanisms of chemical carcinogenesis and to provide a framework on which the mechanisms can be considered. Figure 25 provides such a schema.

Chemical agents that may be carcinogenic are metabolized by endogenous cellular mixed-function oxidase systems. The product(s) of such an event may be "detoxified" and eliminated from the organism. Alternatively, the resultant agent may be transformed into an electrophile that can then interact with a variety of the cellular macromolecules. This material is the proximate or ultimate carcinogen. Other carcinogenic chemicals may not require activation, but act directly as alkylating agents modifying macromolecules, or intercalat-

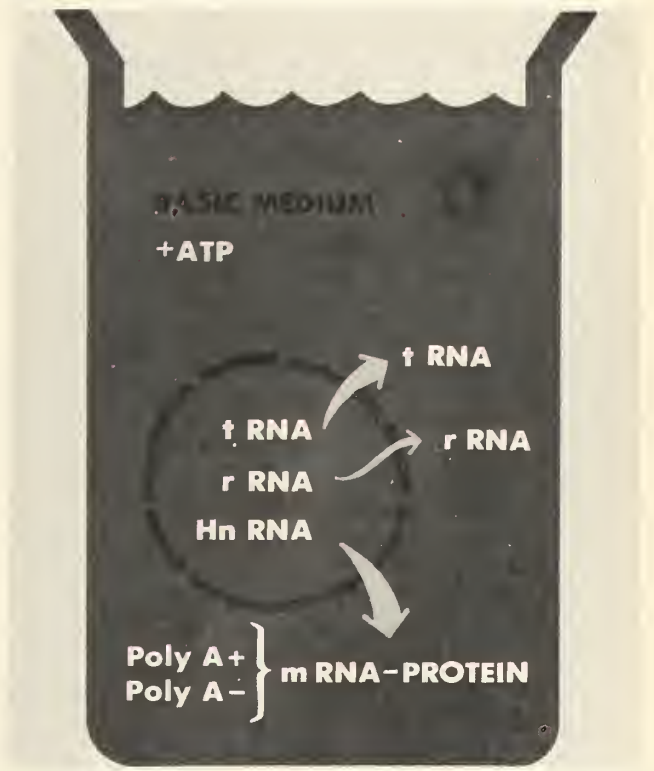

Figure 24.—This diagram shows the in vitro system used for analyzing RNA transport from nucleus to surrogate cytoplasm. RNAs are prelabeled with the in vivo administration of precursors, as orotate, and the nuclei isolated from liver. Suspended in a surrogate cytoplasm consisting of a sucrose-buffered solution, these nuclei release very small quantities of transfer RNA (tRNA). On the other hand, the addition of an energy source, such as adenosine triphosphate (ATP), is associated with a remarkable release of messenger-like (mRNA) species. This system, initially developed by Ishikawa,[101] and currently used in modified form by Webb and colleagues,[102] Agutter[103] and Clawson and associates,[62,97] shows an energy-dependent release of messenger-like species under these circumstances. Nuclei isolated from cancer cells or cells exposed to carcinogens release increased amounts of RNA, also with messenger-like activity, in the absence of added adenosine triphosphate. rRNA = ribosomal RNA, Hn RNA = heterogeneous nuclear RNA, Poly A = polyadenylic acid.

ing between the helical turns of DNA and potentially producing an altered regulation. The macromolecular adduction results in a cellular response. At the extreme the cell dies and the process ceases, or it results in several different modifications of cell behavior. If these cells replicate, several different foci may appear. With replication (and potentially without it), some of these cellular foci will heal themselves, remodeling to normal structures. For reasons that are not clear, however, one or more will autonomously proliferate, forming secondary clones. Some of these clones may revert to normal and others may persist, forming benign neoplasms, or resulting in a proliferative invasive lesion, that is, cancer.

On the basis of the above, the interaction of a carcinogen with a cell resulting in several different altered foci represents an initiation step. There are clearly diverse mechanisms for initiation, not all of which yield a true neoplasm. The promotional event involves cell replication, which results in another population of cells. Subsequent changes within these cell populations also occur. Some of these revert to normal cell types, others to spontaneously proliferating cell populations. From the latter group, different clones seem to be selected that can become truly autonomous and either invasive or noninvasive. The selection of the subtypes following initiation is probably still the most poorly understood part of the process. Apparently the agents that can act as initiators and promoters are many and appear to have multiple effects. This being the case, a simple explanation for transformation is not available.

Implications for Humans

Undoubtedly several chemical, physical and viral agents are able to produce malignant disease in humans.

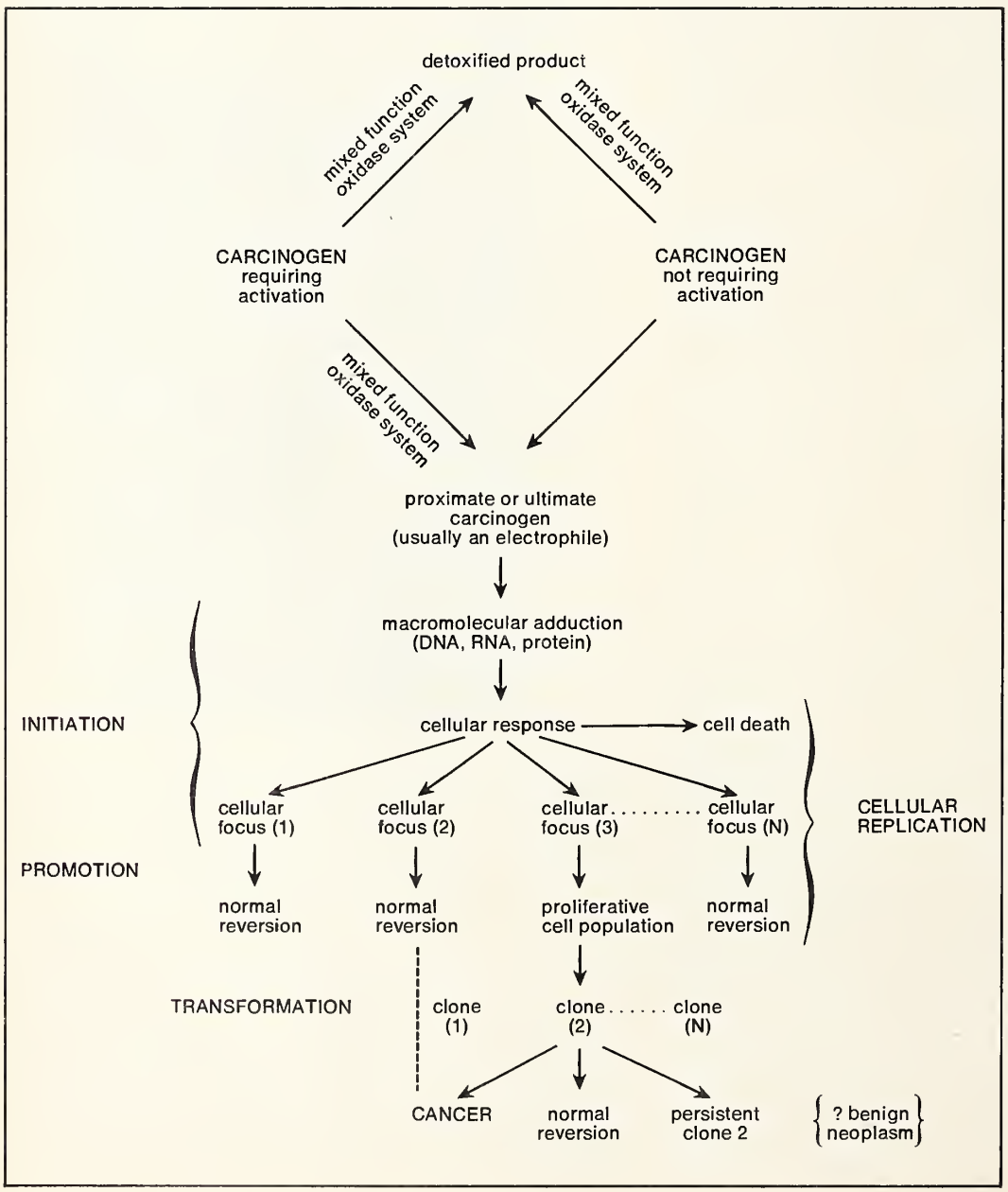

Figure 25.—This is a proposed scheme of chemical carcinogenesis. The agent, either with or without activation, interacts with cellular macromolecules. The target cells are perturbed; some die and others respond to the chemical modification in different ways. This represents a promotional event. These several cell populations may then be stimulated to replicate, during which foci of diverse cellular clones arise. During this process, a reversion to "normal" may take place. On the other hand, a replicating clone can arise—a promotional event. From this latter group a second subset may appear, one that becomes truly autonomous. If these cells invade, they produce cancer. If they remain localized, they produce a benign neoplasm.

The observation that a single exposure may be enough to initiate a recipient cell population in which cancer can develop is of major concern in regulating exposure. Identifying a complex series of events that may or may not include mutation must be carefully considered lest we opt immediately for mutational assays as potential survey mechanisms for carcinogens. Our increasing technical ability to measure smaller and smaller perturbations of chemical interactions with cellular components has not kept pace with our understanding of their significance.[106] The use of monoclonal antibodies to detect adduction can well determine *exposure* of humans and mice to chemical agents that alkylate nucleic acids. This does not provide information about the *risk* of this change, or even whether or not a risk exists.* Dire predictions of the decimation of the human race by carcinogens have fortunately not come to pass. In fact, a critical analysis of the incidence of age-matched human disease suggests that with one exception the occurrence of cancer has changed only modestly,[107-109] (Figure 26) with some cancer actually decreasing in frequency. The one major exception is cancer of the lung, a disease clearly related to cigarette smoking. It is appropriate to point out, however, that none of the studies using animals have so far been able to reproduce this particular disease. Cigarette smoking seems to be a human hazard, much as alcohol is a human poison. Chemicals do cause cancer. Identification of the mechanisms by which they do so will undoubtedly yield new information concerning regulatory mechanisms in molecular biology. It is unfortunate that 200 years after finding the chemical association of cancer in humans, our understanding still does not give us any more than a clue to the mechanisms involved.

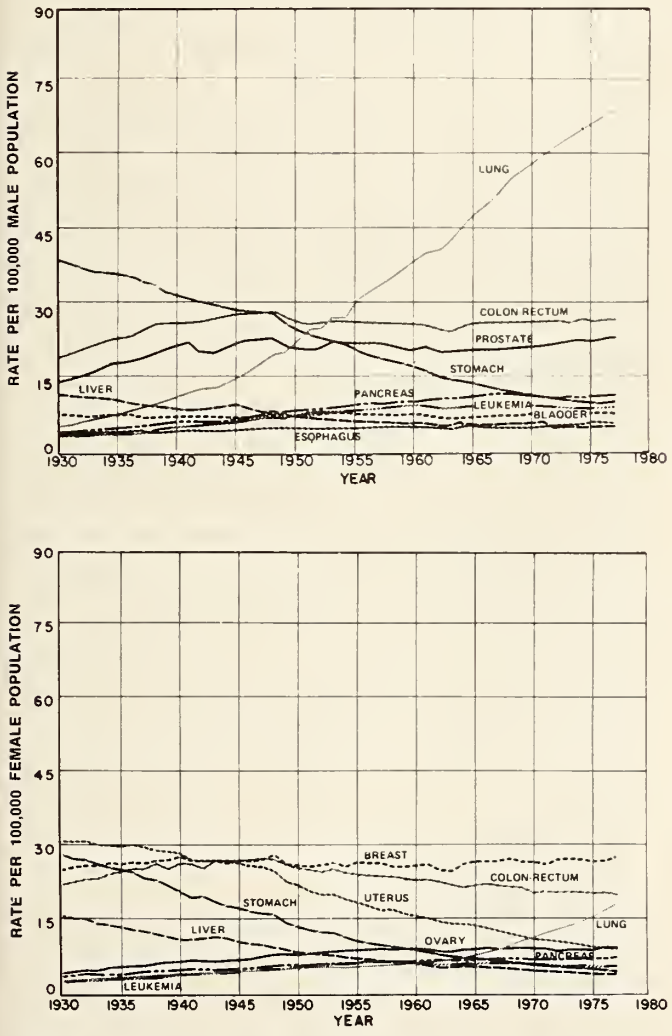

Figure 26.—Cancer death rates in men **(A)** and cancer death rates in women **(B)** by site in US population, 1930 through 1977 (rate standardized for age on the 1970 population). Note the only significant and pronounced change in cancer incidences is of the lung in both men and women. Sources of data: National Vital Statistics Division and Bureau of the Census, United States. (Reprinted with permission from *Ca—A Cancer Journal for Clinicians,* Vol 31, No. 1, © 1981, American Cancer Society, Inc.)

*Dr Emmanuel Farber has emphasized that both risk and exposure must be established. Simple exposure may or may not establish a risk. Identifying exposure without quantifying risk can result in a large number of anxious persons.[11]

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Medical Staff Conference

Osteoporosis

Part I

Advanced Radiologic Assessment Using Quantitative Computed Tomography

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *This Medical Staff Conference is a symposium on osteoporosis, a disease whose prevalence is increasing in proportion to the growing number of elderly women in our population. Dr Harry Genant will open the discussion with a review of the radiologic methods used to detect metabolic bone disorders. In Part II Dr Gilbert Gordan will discuss the effectiveness of estrogen replacement therapy in preventing bone loss and fractures in elderly women and Dr Philip Hoffman will review the risks of menopausal estrogen therapy.*

DR GENANT:† Osteoporosis is a common disorder affecting large numbers of adults and resulting in considerable morbidity, mortality and public health expenditure.[1,2] Many methods have been developed for quantitatively assessing the skeleton so that osteoporosis can be detected early or its progression and response to therapy can be carefully monitored. The selection of anatomic sites and of methods for quantifying skeletal mass is of great importance. The skeleton as a whole is composed of about 80% cortical or compact bone and 20% trabecular or cancellous bone.[3] The spine is composed of about two-thirds cancellous (less in the elderly) and a third compact bone in the dense endplates and posterior elements. Trabecular bone has a high turnover rate, about eight times that of compact bone, partly as a result of its high surface-to-volume ratio. This high turnover rate makes trabecular bone a sensitive measuring site that is highly responsive to metabolic stimuli, which probably accounts for the clinical observation that osteoporotic fractures occur first in the vertebral bodies or distal radius, areas of predominantly trabecular bone.

The most widely used noninvasive methods for determining bone mineral content are radiogrammetry[4] and photon absorptiometry,[5] which measure primarily cortical bone of the peripheral appendicular skeleton. Techniques developed as research tools include Compton scattering,[6] which measures primarily peripheral trabecular bone, and dual photon absorptiometry[7] and neutron activation analysis,[8,9] which measure an integral of cortical and trabecular bone in the axial or whole skeleton. More recently, computed tomography (CT)[10-23] has been advanced as a method of measuring purely trabecular bone in the axial or peripheral skeleton. To date no single method has proved entirely satisfactory in evaluating metabolic bone disease; often more than one technique applied to several anatomic sites provides the most meaningful assessment.

Appendicular Cortical Bone Measurements

Peripheral appendicular mineral content is relatively easy to measure and the techniques are widely available. These measurements are of limited diagnostic usefulness in patients who have osteoporosis, however, because they overlap considerably with those in control populations, and because peripheral cortical values do not necessarily correlate with those in the spine.[24]

Radiogrammetry

The simple measurement of cortical thickness from a radiograph using a caliper or reticle is easy to do, is

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This is Part I of a two-part Medical Staff Conference. Part II will appear in a subsequent issue.

reproducible and is backed by a large body of normative data.[4] This technique (most commonly applied to the metacarpal shafts) lacks sensitivity for assessing many metabolic bone disorders because it reflects only endosteal bone resorption. Intracortical resorption (cortical porosity) and trabecular bone resorption, which are important indices of high turnover states, are not measured.

Single Photon Absorptiometry

A widely used and more precise technique is photon absorptiometry using an iodine 125 source interfaced with a sodium iodide scintillation detector. While many such devices have been used, the most widely accepted is the Norland-Cameron, which measures the radial shaft, though other tubular bones can be examined.[5,25] Considerable normative data are available and many studies have supported the usefulness of the device in clinical research. A reproducibility of 2% and an accuracy of about 6% have been shown. The measurement is primarily an integral of cortical bone because the diaphysis, where measurements are generally made, contains little cancellous bone. The metaphysis, which contains proportionately more trabecular bone (up to 25% to 50% of total integral bone) is more difficult to measure due to repositioning errors.[26] Consequently, precision may be poor at this site. A major limitation of the photon absorptiometric technique is that it reflects the state of peripheral tubular bones and measures primarily cortical bone. These measurements do not necessarily reflect the overall skeletal status of an individual patient and are therefore of restricted diagnostic value.[16,24]

Axial Mineral Measurements

Because of the limitations of techniques that measure mineral content in peripheral bones, several methods have been developed that accurately and diagnostically measure mineral content in the spine.

Dual Photon Absorptiometry and Neutron Activation Analysis

Dual photon absorptiometry[7,27,28] and neutron activation analysis[9] have been studied extensively as possible techniques to measure spinal mineral, both measuring *integral* vertebral bone, a summation of compact and cancellous bone. In the dual photon absorptiometry technique reported by Madsen and co-workers,[7] a high-purity, high-activity gadolinium source—which has photons of predominantly 44 kiloelectron volts (keV) and 100 keV—is used as the transmission source. The scans are done on a modified whole body rectilinear scanner and take about 45 minutes to complete. The precision of measurement in healthy young controls is 2% to 3% (coefficient of variation). The accuracy in phantoms of dipotassium hydrogen phosphate solutions is 1% to 2% (standard error of estimate)[7] and in vertebral specimens is about 10%.[27]

In vivo neutron activation analyses have been under investigation at several centers for the past decade.[8,9,29] In this method, neutrons bombard a small fraction of the total calcium 48 in the body, producing calcium 49 (half-life of 8.8 minutes), which is then counted externally. The neutrons—with energies of 1 to 15 million electron volts (meV)—are derived from accelerators, reactors or α-neutron sources. The technique provides an estimate of bone mineral content because, at least in the skeleton, calcium makes up a constant fraction (0.395) of the mineral. Radiation doses for such measures range from 200 to 3,000 mrem, depending on the neutron energy and the detector efficiency. Recent studies suggest precision and accuracy on the order of 2% to 5%.

But the lumbar vertebrae contain substantial amounts of compact bone, mostly in the laminae, pedicles and dense vertebral endplates,[3] and only part of the mineral measured is "high-turnover" trabecular bone with high sensitivity to metabolic stimuli. In addition, vertebral compressions, hypertrophy of articular facets, discogenic sclerosis or marginal osteophytosis, and extraosseous calcification, which are widespread in elderly people, may cause inaccurate and poorly reproducible integral vertebral mineral measurements.

Spinal bone mineral content is measured by dual photon absorptiometry or neutron activation analysis only at a few research centers. The use of neutron activation analysis is likely to remain limited because of the technical problems involved in development, standardization and reduction of patient dose. The potential exists for broader application of dual photon absorptiometry; however, it may not be possible for a hospital to provide the space or funds for special instrumentation devoted solely to bone mineral analysis. Furthermore, relative to computed tomography, the poor sensitivity and lack of availability of dual photon absorptiometry may limit its clinical distribution.

Computed Tomography for Bone Mineral Analysis

Computed tomography has been widely investigated in recent years as a noninvasive means of determining quantitative bone mineral content. The usefulness of computed tomography for measuring bone mineral content lies in its ability to provide a quantitative image, permitting measurement of trabecular, cortical or integral bone, centrally or peripherally. Thus, a potential major advantage of computed tomography over photon absorptiometry or neutron activation analysis is the capability of precise regional localization and of spatial separation of highly sensitive cancellous bone from less responsive cortical bone.[15]

Quantitative computed tomography measures changes in trabecular mineral content in the spine[11-13,16-19] and in the radius[15,20,22,23] with great sensitivity and precision. The extraction of this quantitative information from a CT image requires sophisticated calibration and positioning techniques.[16] Rapid technologic advances in CT, however, especially in external localization capabilities, mean that many of the CT scanners worldwide may be modified for quantitative CT measurements at relatively little cost.[17,18] Reduced patient time, radiation

exposure and cost make this an attractive technique for widespread application of noninvasive bone mass measurements.

Quantitative CT Methods for Determining Vertebral Mineral Content

At the University of California, San Francisco (UCSF), vertebral mineral content is measured on a rotary fan-beam scanner (General Electric CT/T 8800 or CT/T 9800) by methods developed conjointly with Christopher E. Cann, PhD. Mineral content is measured in the midportion of the upper lumbar vertebral bodies. These standard measuring sites are chosen for the following reasons: (1) A close correlation between cancellous mineral content in adjacent vertebrae eliminates the need for a large number of measurement sites, (2) the availability of a large measuring volume for cancellous bone reduces variation from intravertebral inhomogeneities and eliminates partial-volume averaging of the dense endplates and (3) these sites avoid the lower lumbar vertebrae, wherein degenerative disease with reactive sclerosis may affect the measurement.

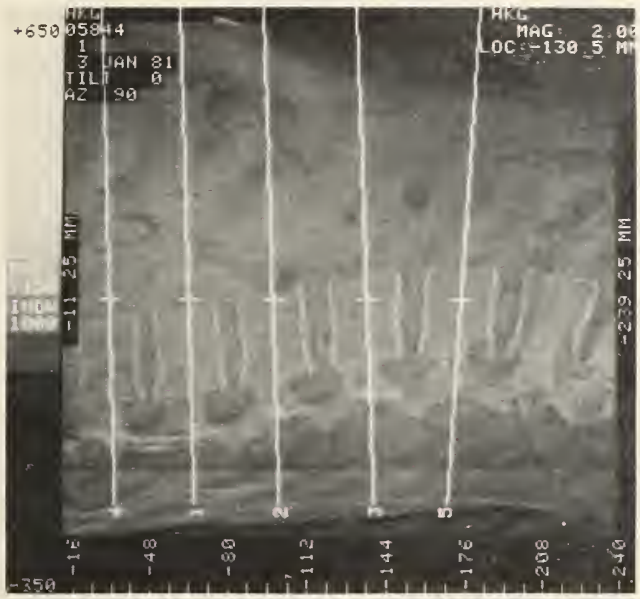


Figure 1.—A lateral scout view provides a rapid and simple localization approach in which the midplane of four to five vertebral bodies is defined on a video monitor and a single 1-cm-thick section is obtained at each level.

Figure 2.—An oval region of interest within a midvertebral body is used to determine cancellous bone mineral content, while circular regions of interest are used to quantify the calibration solutions.

Localization and Scanning Procedures

Two different localization and scanning procedures can be used. In the first, our standard technique, the patient is positioned by means of a computed tomographic localization system, so that the first axial slice is of the bottom of T-12 and the last is of the top of L-3. About 18 contiguous 5-mm-thick slices

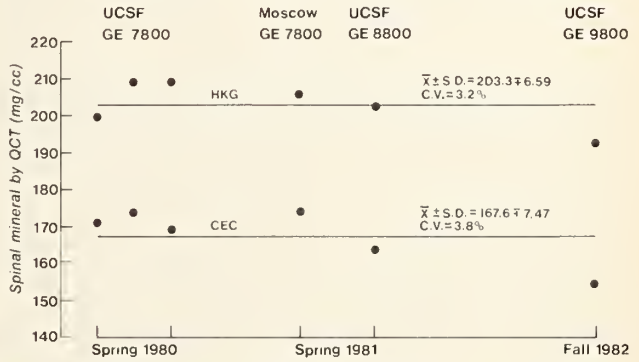


Figure 3.—Spinal quantitative computed tomographic (QCT) reproducibility: a coefficient of variation (C.V.) between four different scanners—three from University of California, San Francisco (UCSF) and one from Moscow—of 3% to 4% was found for two persons (HKG and CEC), indicating that normative data and clinical results obtained on a scanner at one center may be extrapolated to those obtained at different centers.

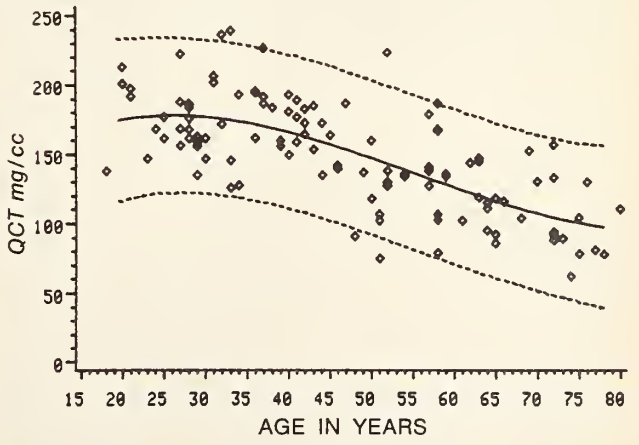


Figure 4.—Vertebral cancellous mineral content in normal men by quantitative computed tomography (QCT) with the use of a cubic regression with 95% confidence intervals, only a slightly better fit to the data for men than a linear regression ($P<0.15$).

are obtained using rapid, dynamic scanning at 80 kilovolt(peak) (kV[p]) covering the region of the L-1 and L-2 vertebral bodies. Precise positioning to the midplanes of L-1 and L-2 is obtained with advanced image analysis software using a specially programmed off-line computer.[11,16]

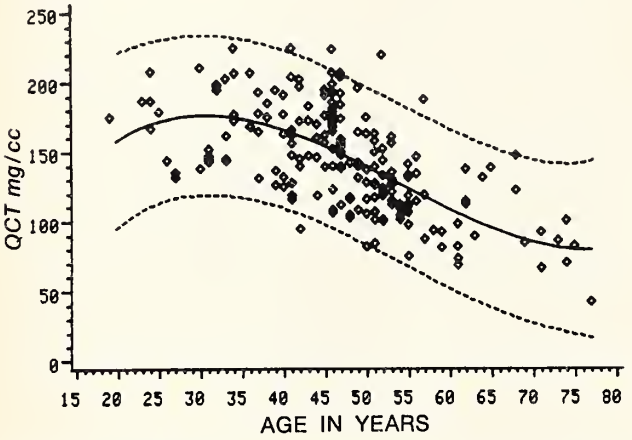


Figure 5.—Vertebral cancellous mineral content in normal women by quantitative computed tomography (QCT) with the use of a cubic regression with 95% confidence intervals.

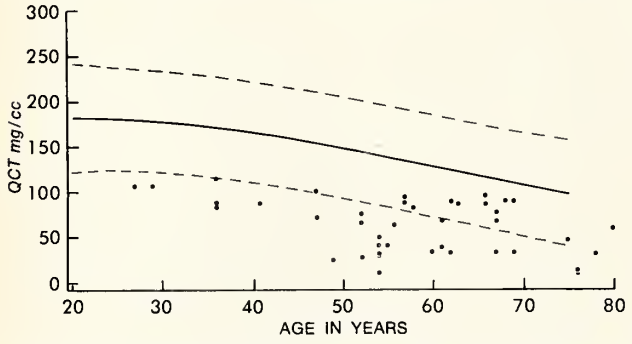


Figure 6.—Quantitative computed tomography (QCT) values for men who have idiopathic osteoporosis and spinal fractures (•) plotted against the normal male curve (cubic regression with 95% confidence intervals). A fracture threshold of about 105 mg per cc is evident.

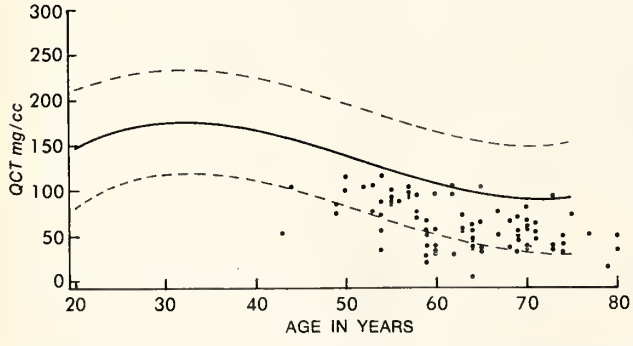


Figure 7.—Quantitative computed tomography (QCT) values for women who have postmenopausal osteoporosis and spinal fractures (•) plotted against the normal female curve (cubic regression with 95% confidence intervals). A fracture threshold of about 105 mg per cc is evident.

A second simpler and readily available localization and scanning approach (Figure 1) also uses the computed radiographic system to take a lateral scout film of the lumbar spine.[17] Using cursor-determined coordinates, the midplane of four vertebrae is identified, and a single 1-cm-thick slice is obtained at each level. Thus, four separate volume elements for quantifying and averaging are rapidly obtained using this technique. Normalization and expression of data are the same for both approaches.

Calibration and Data Analysis

Calibration against scanner drift is provided by a special crescent-shaped normalization phantom on which the patient lies during the scanning procedure (Figure 2). The phantom contains solutions of dipotassium hydrogen phosphate (mineral equivalent), ethanol (fat), glycerol and water (soft tissue) for calibration.[15] Analysis for mineral content is done using an oval region of interest to determine the mean CT number in a 4-cc volume within each vertebral body. The CT numbers derived from the calibration phantom scanned simultaneously with the patient are then used to calculate the mineral equivalent for each vertebra.

Precision and Accuracy

Clinical application of bone-mass quantification places requirements on the reproducibility and accuracy of any measurement technique. The precision or reproducibility for in vivo vertebral mineral determination in human subjects is 1.6% (coefficient of variation) when the calibration procedure and the advanced software for localization are used.[17] The reproducibility is reduced to about 2% to 3% when the simpler external location technique is used, but this approach can be readily applied to most advanced CT scanners and does not require special software. With either technique, patient time on the scanner table is about 10 to 15 minutes and total radiation dose to the upper abdomen is 100 to 200 mrem.[11,18]

The most important factors governing the accuracy or reliability of computed tomography for vertebral mineral determination are the absolute accuracy of the CT numbers that are calculated by the scanner and the chemical composition of the vertebral bone mixture. Recent improvements in beam-hardening corrections in some of the newer CT scanners can reduce the error in the CT number to less than 2% for trabecular bone mixture in the lumbar spine. The use of empiric corrections, determined for each scanner, can further reduce the error for measuring the CT number in the lumbar spine. The accuracy of CT mineral determination in phantoms containing potassium phosphate solutions is 1% to 2%,[15] in monkey vertebrae in vivo is about 5%[12] and in human vertebrae spanning a wide age range is 8%.[19]

Accuracy may be reduced, however, in elderly persons who have osteoporosis. The vertebral bone mix-

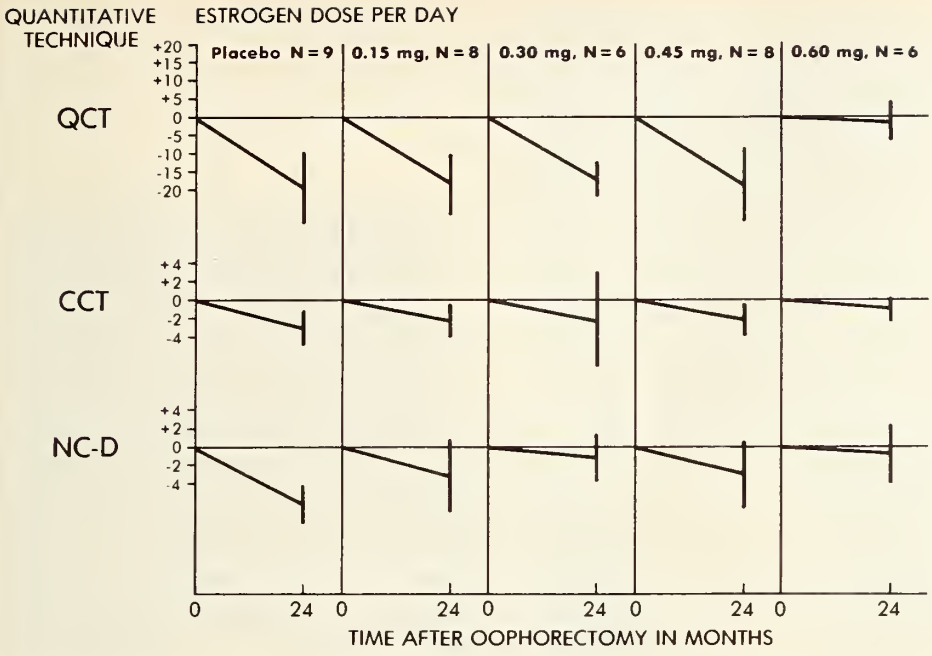


Figure 8.—The mean percentage of bone mineral loss (± standard deviation) at 24 months is shown as a function of treatment group and quantitative technique. QCT = quantitative computed tomography, CCT = combined cortical thickness, NC-D = Norland-Cameron densitometry.

ture is composed of three components—hematopoietic marrow (soft tissue), fat and bone—in varying concentrations. Because the density of fat is less than that of soft tissue, it reduces the measured CT number (x-ray attenuation, or density) of the spine by about 12 Hounsfield units per 10% of fat by weight. This can produce an apparent decrease in the high-density bone mineral if the amount of fat is large and the amount of bone is very small. For example, the error at 80 kV(p) for a patient who has a mineral equivalent value of 150 mg per cc is about minus 5% per 10% of fat by volume. Dual-energy CT, using preprocessing or postprocessing techniques,[10,14,15] can reduce the magnitude of this error to 1% to 2%. It may not be necessary for most clinical application, however.

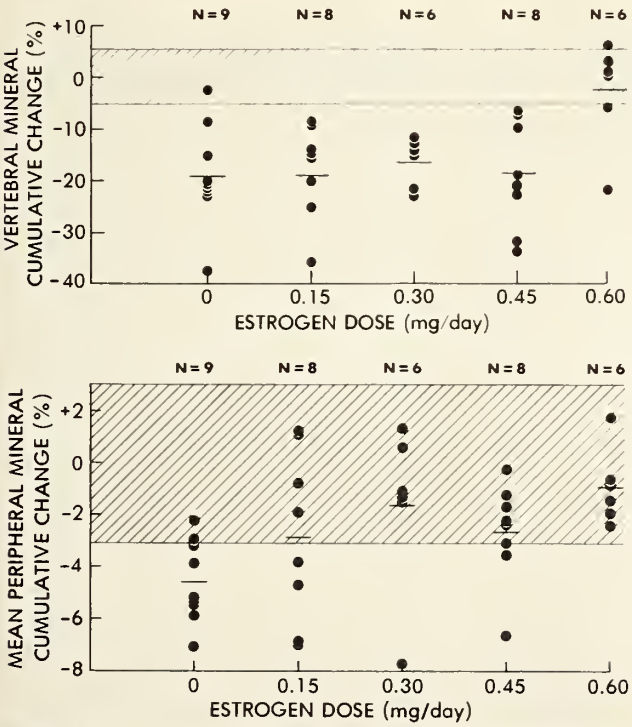


Figure 9.—The estrogen dose-response relationships determined by vertebral mineral **(top)** and mean peripheral cortical **(bottom)** measurements for individual women at 24 months after oophorectomy. The cross-hatched regions represent no significant change—that is, those greater than twice the coefficient of variation or precision of measurement.

Scanner Independence: Distribution of Quantitative CT Techniques

We have assessed the scanner independence of vertebral quantitative CT measurement by determining the interscanner variability on four separate CT scanners using these techniques (Figure 3). A coefficient of variation between scanners of 3% to 4% was found,

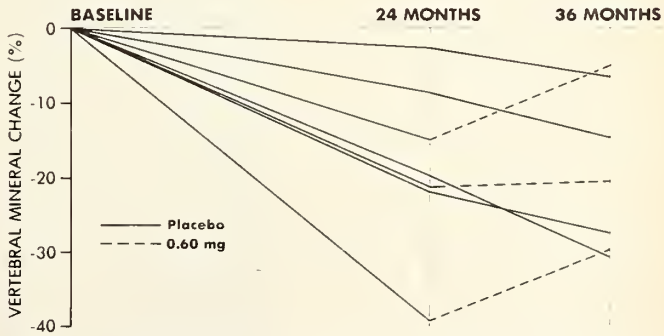
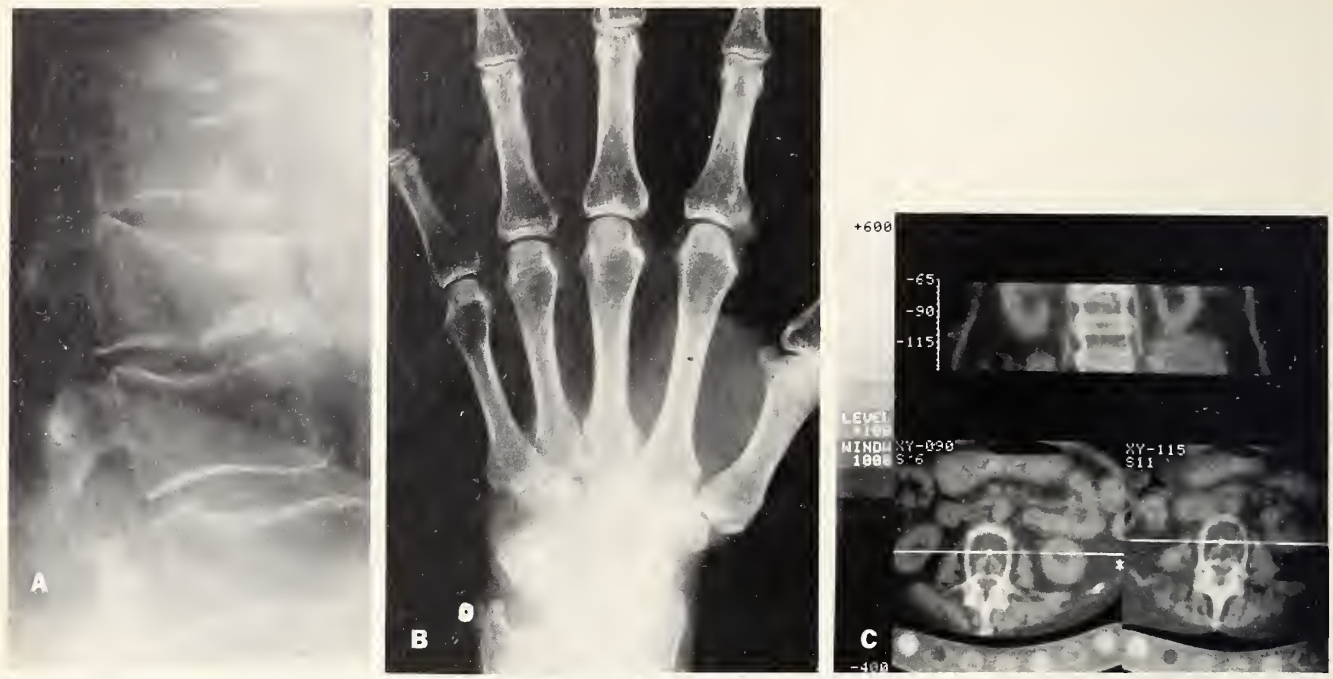


Figure 10.—Percentage of vertebral mineral change at 24 and 36 months after oophorectomy. The four women treated with placebo for 36 months lost spinal mineral at a mean rate of 6.6% a year for the first two years, and continued to lose at 7.2% a year the third year. The three women crossed over at 24 months to conjugated estrogen, 0.6 mg a day, lost spinal mineral at a mean rate of 12.5% a year for the first two years and regained bone at a mean rate of 7.37% the third year.



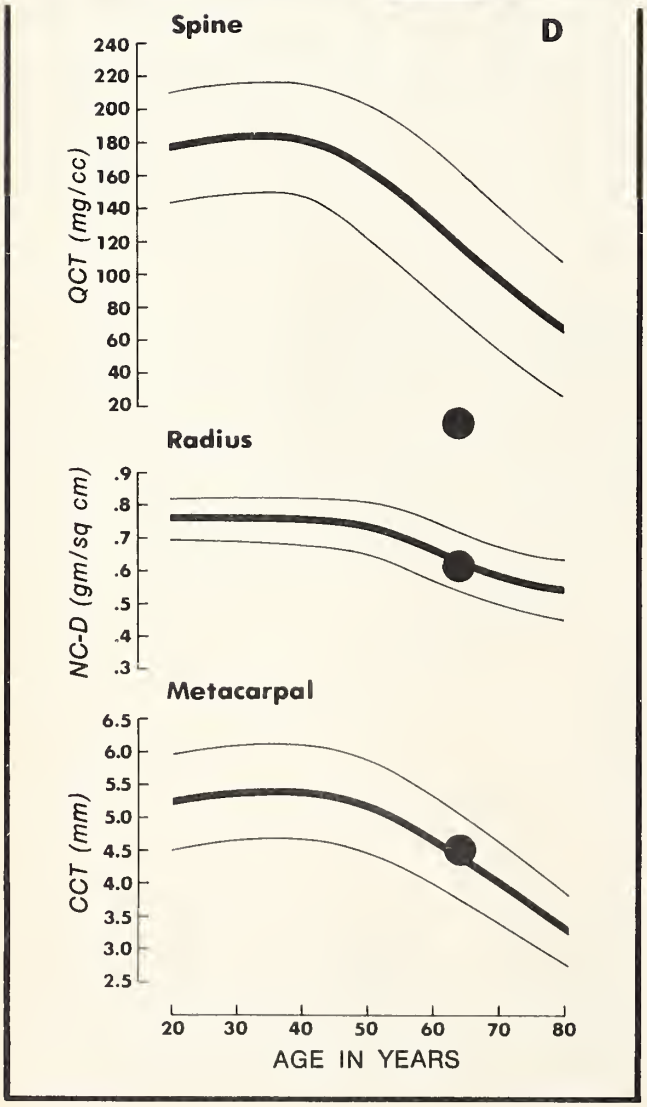


Figure 11.—Studies done in a 59-year-old woman with postmenopausal osteoporosis. **(A)** The radiograph of the thoracolumbar spine shows advanced osteoporotic vertebral fractures. **(B)** The radiograph of the hand shows grossly normal mineralization of the cortices and mild periarticular demineralization. **(C)** Qualitatively, computed tomography shows prominent lucency of the vertebral spongiosum. **(D)** By quantitative computed tomography (QCT), Norland-Cameron densitometry (NC-D) and combined cortical thickness (CCT), there are severe osteopenia of the axial skeleton and normal mineralization of the peripheral appendicular skeleton for age and sex (± standard deviation).

indicating that normative data and clinical results from a scanner at one center may be extrapolated to those from different centers.

Currently, vertebral mineral determination by quantitative CT has been implemented at 50 centers widely distributed geographically (United States, Canada, England, France, Belgium, the Netherlands, Germany, Japan and Australia) and representing a wide array of commercial scanners (General Electric, Siemens, Picker, Philips, Technicare and CGR). With a worldwide distribution of about 1,500 advanced CT body scanners, the capability now exists for widespread application of vertebral bone mineral determination by quantitative computed tomography.

Clinical Applications of Quantitative Computed Tomography

These quantitative CT techniques for vertebral mineral determination have been used to study skeletal changes in cases of osteoporosis and other metabolic bone diseases in collaboration with Drs Felix O. Kolb, Bruce Ettinger, Gilbert S. Gordan and Claude Arnaud. Longitudinal and cross-sectional bone mass measurements have been done at UCSF in more than 1,500 patients seen clinically or in research programs, and the results presented here show the use of quantitative CT

spinal mineral measurement in delineating normal and osteoporotic populations, in serially assessing skeletal response to treatment and in diagnosing metabolic bone diseases.*

Cross-sectional Studies of Normal Volunteers and Patients

A group of 320 men and women, ages 18 to 80, was used to define the normal mean and range of vertebral cancellous mineral content as a function of age for men and women. All persons were ambulatory, had no history of chronic debilitating illness or recognized calcium metabolic disorders and no vertebral fractures as assessed by lateral spinal radiographs. This normal population included volunteer subjects and Caucasian or Asian patients referred for CT scans of the abdomen or spine in whom chronic disease and metabolic disorders were excluded. The values for normal men (Figure 4) and normal women (Figure 5) are plotted as a function of age, with the mean and 95% confidence intervals shown, using a cubic regression. The normal mean value for control men is about 175 mg per cc in the age range of 20 to 40 years. With increasing age, there is normally a gradual loss of mineral, so that by age 70 the mineral content is reduced by 40% to about 110 mg per cc. The normal premenopausal mean value for mineral content in women is also about 175 mg per cc in the age range of 20 to 40 years. Starting at 40 to 50 years of age vertebral mineral content decreases, initially rapidly, so that by age 70 mineral content in normal women is reduced by 50% to about 90 mg per cc.

Fracture Threshold

Studies of men and women who have osteoporosis, defined by the development of atraumatic fractures, show an approximate fracture threshold above which osteoporotic fractures are rare and below which fractures are common. For both men (Figure 6) and women (Figure 7) spinal compression fractures generally occur when quantitative CT mineral values fall below about 105 mg per cc.

Longitudinal Studies of Postoophorectomy Bone Loss

A small group of premenopausal women who had recently undergone total hysterectomy and oophorectomy was studied in a serial fashion to determine bone mineral changes in the axial and peripheral skeleton after loss of ovarian function.[13,16-18] They received either a placebo or conjugated estrogen (Premarin), in doses ranging from 0.15 to 0.60 mg per day, to determine the minimum vertebral osteotrophic dose of estrogen. Previous work by Lindsay and associates[30] and Recker and colleagues[31] showed that the equivalent of 0.6 mg of other estrogen compounds prevented postmenopausal bone loss in the peripheral skeleton.

Bone mineral measurements were made at 0, 6, 12,

*Denice Nakano assisted in performing quantitative techniques. Helen Chen, Liv Ax and Cynthia Hayashi assisted in patient selection, scheduling and coordinating the clinical activities.

Figure 12.—Studies done in a 50-year-old man with Cushing's disease. **(A)** The radiograph of the lateral lumbar spine shows pronounced osteoporosis with vertebral collapse and marginal condensation of the endplates. **(B)** The radiograph of the hand shows normal mineralization of the cortices. **(C)** By quantitative computed tomography (QCT), Norland-Cameron densitometry (NC-D) and combined cortical thickness (CCT), severe osteopenia of the axial skeleton and normal mineralization of the peripheral appendicular skeleton are recorded (± standard deviation).

24 and 36 months of treatment. In addition to spinal quantitative CT, two separate measures of peripheral cortical bone were made as follows: (1) combined cortical thickness of the second metacarpal midshafts[4] and (2) Norland-Cameron photon absorptiometry[5] of the radial diaphyses.

The results by quantitative CT of the spine, radiogrammetry of the metacarpal cortices and photon absorptiometry of the radial diaphyses are shown in Figure 8. The magnitude of bone mineral loss in the placebo and low-dosage treatment groups was far greater by vertebral quantitative computed tomography than by either of the peripheral cortical measurements. The bone-loss value determined in the peripheral skeleton by radial photon absorptiometry was greater than that by metacarpal radiogrammetry.

The correlation between mean peripheral cortical bone loss (average of combined cortical thickness and photon absorptiometry) and vertebral cancellous bone loss was significant ($r=0.581$, $P<0.01$) for the group as a whole, but considerable dispersion about the regression line precluded an accurate prediction of spinal loss from peripheral measurements for individual patients. The slope of the regression line indicated more than a sevenfold greater bone mineral loss from the spinal spongiosum than from the appendicular cortex.

The estrogen dose-response relations, determined by vertebral mineral measurement and by mean peripheral measurement, are shown for individual patients in Figure 9. By quantitative CT, a significant two-year spinal loss (more than 5.6% or twice the coefficient of variation) was seen in all but one woman receiving less than 0.6 mg of conjugated estrogen daily. In contrast, significant mean peripheral loss (more than 3.2% or twice the coefficient of variation) was seen principally in women receiving placebo or 0.15 mg per day of conjugated estrogen.

Preliminary data for the seven women who initially received placebo and who completed three years of analyses suggest that adequate doses of estrogen may reverse the vertebral bone loss (Figure 10).

Diagnostic Studies in Selected Metabolic Bone Disorders

For diagnostic applications and to monitor therapy in the clinical setting, a "complete bone densitometry" study is done. This examination includes high-resolution radiographs of the hands, a lateral radiograph of the thoracolumbar spine, combined cortical thickness measurement of the metacarpal shafts, photon absorptiometry of the radius, and vertebral quantitative computed tomography. The clinical results of radiographic and quantitative analyses of the axial and peripheral skeleton in a number of common metabolic bone disorders are shown in Figures 11 to 14. Examples are given of cases of postmenopausal osteoporosis, Cushing's syndrome, renal osteodystrophy and fluorosis. The necessity of measuring at several skeletal sites to detect or monitor disease is underscored by the poor corre-

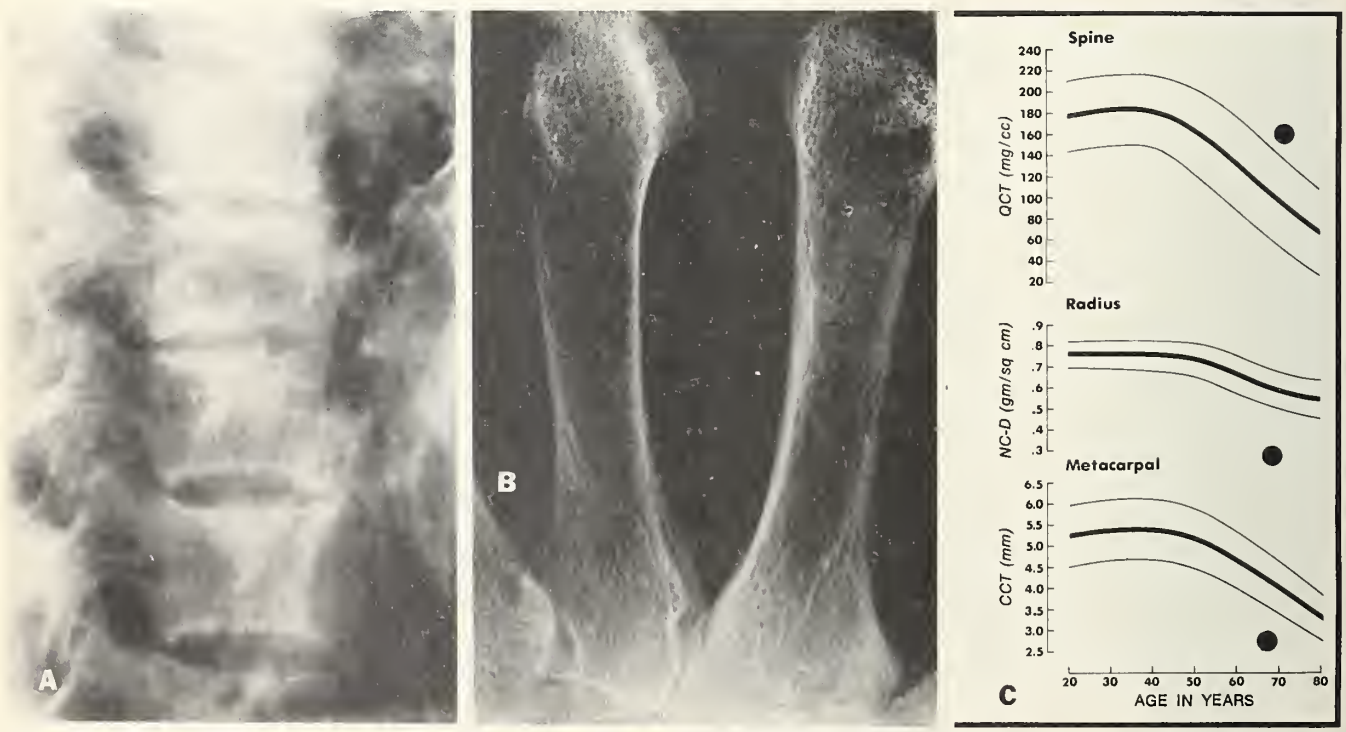


Figure 13.—Studies in a 69-year-old woman with renal osteodystrophy. **(A)** The radiograph of the thoracic spine shows mild osteosclerosis of the spongiosum. **(B)** A magnified radiograph shows severe demineralization of the metacarpals accompanied by increased intracortical bone resorption. **(C)** By quantitative computed tomography (QCT), Norland-Cameron densitometry (NC-D) and combined cortical thickness (CCT), increased mineralization of the axial skeleton and severe demineralization of the peripheral appendicular skeleton are recorded (± standard deviation).

lation betwen spinal trabecular and peripheral cortical bone mass in some patients. For example, in the relatively common disorder of postmenopausal osteoporosis (Figure 11) and the less common idiopathic osteoporosis, it is not unusual to find pronounced demineralization of the axial skeleton while the peripheral skeleton remains normal for age and sex. Similarly, disproportionate loss of cancellous compared with cortical bone in response to corticosteroid excess (Figure 12) is reflected by a large reduction in vertebral mineral content compared with appendicular cortical mineral content. Conversely, prominent demineralization of the peripheral cortex in cases of renal osteodystrophy (Figure 13) may be accompanied by sclerosis of the vertebral cancellous bone, producing a "Rugger-Jersey" spine—that is, having horizontal bands of sclerosis. Similarly, treatment of osteoporosis with sodium fluoride (Figure 14) may result in remineralization of the spinal cancellous bone, while the peripheral cortical skeleton remains largely unchanged.

Summary

It can be concluded that measurements of peripheral *and* axial as well as compact *and* cancellous bone provide the best overall assessment of skeletal status in many metabolic disorders. The greatest advantages of spinal quantitative computed tomography for noninvasive bone mineral measurement lie in the high precision of the technique, the high sensitivity of the vertebral cancellous measurement site and the potential for widespread application. The clinical results presented herein suggest that quantitative computed tomography provides clinicians with a powerful new tool to evaluate and monitor the many forms of osteoporosis and its various treatments.

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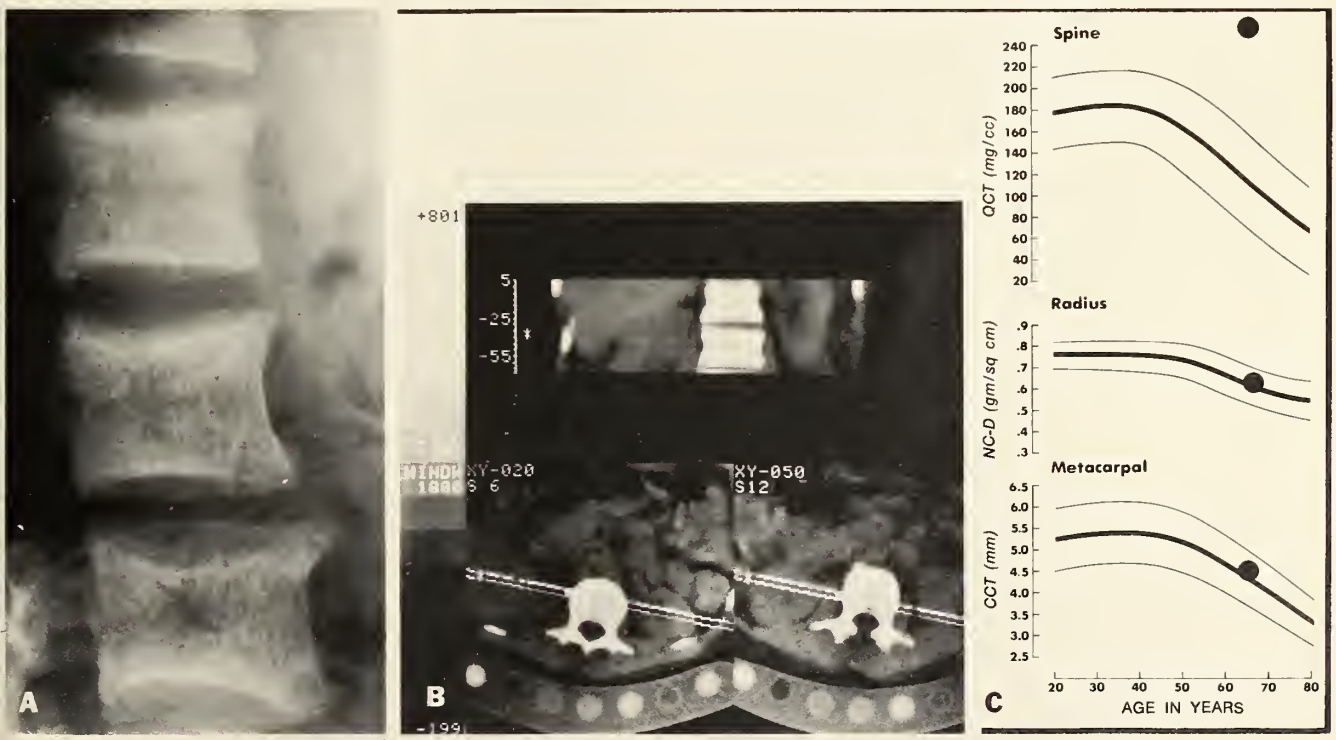

Figure 14.—Studies done in a 67-year-old woman with sodium fluoride-treated osteoporosis. **(A)** A radiograph of the lumbar spine shows pronounced sclerosis of the spongiosum (whereas the hand showed no osteosclerosis). **(B)** A computed tomographic study qualitatively shows densely sclerotic vertebral bodies. **(C)** By quantitative computed tomography (QCT), Norland-Cameron densitometry (NC-D) and combined cortical thickness (CCT), greatly increased mineralization of the spine and normal mineralization of the peripheral appendicular skeleton are recorded (± standard deviation).

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Articles to Read in Other Journals

Risk of Uterine Perforation Among Users of Intrauterine Devices

Heartwell SF, Schlesselman S

Obstetrics & Gynecology
61:31-36, Jan 1983

DISCIPLINES: Family Practice, Obstetrics, Gynecology, Planned Parenthood, Public Health

READABILITY: Very good

In this collaborative Women's Health Study the authors concluded that when an intrauterine device of any type was inserted into the uterus of a lactating mother, perforation was ten times as frequent as when this was done in nonlactating women. The reason: low estrogen endometrium and increased uterine contractility.

—E. R. W. FOX, MD
Coeur d'Alene, Idaho

Epitomes
Important Advances in Clinical Medicine

Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St, San Francisco, CA 94103

Neonatal Abdominal Ultrasonography

THE ABDOMEN, pelvis, heart and head of a newborn infant are readily imaged with high-frequency small parts ultrasound equipment. Real-time ultrasonography equipment is portable, allowing rapid evaluation of a nonsedated fragile neonate in an intensive care nursery.

The most common abdominal masses in newborn infants are of renal origin. Ureteropelvic junction obstruction and resultant hydronephrosis, multicystic dysplastic kidneys, renal vein thrombosis and renal tumors comprise the bulk of these masses. A normal neonatal kidney has decreased renal sinus echogenicity, vis-à-vis an adult kidney, prominent medullary pyramids and an accentuated corticomedullary junction. Echogenicity of a newborn renal cortex is often greater than that of an adult and may equal or exceed that of adjacent liver or spleen. Ultrasound studies easily distinguish between renal masses and nonrenal masses. A multicystic dysplastic kidney has multiple renal cysts located in the region of the kidney, without evidence of a normal renal pelvis or renal parenchyma. Such an appearance is easily distinguished from the dilated fluid-filled pelvis and communicating calyces of a hydronephrotic kidney. The elongated, distended extrarenal pelvis in a ureteropelvic junction may simulate a dilated ureter and the distal ureterovesical junction should be imaged in all cases of hydronephrosis to better delineate the nature of the lesion. The kidney in cases of renal vein thrombosis is usually enlarged and has increased or decreased echogenicity and areas of parenchymal inhomogeneity. Thrombosis is often shown in the renal vein itself and Doppler flow analysis of renal vein patency may offer additional benefits in detecting renal vein thrombosis.

A normal neonatal adrenal gland is readily found using coronal scanning. The right gland is identified in 97% of neonates and the left in 83%. The neonatal adrenal gland is characterized by a thin echogenic core surrounded by a thick rim of sonolucency. The ability to detect adrenal hemorrhage and tumors in neonates has been well described.

The normal neonatal liver, venous anatomy both portal and hepatic and the gallbladder and biliary tract are easily visualized. Gallbladder length, width and width-to-length ratios are unreliable criteria for separating normal from pathologic gallbladders. Gallbladder sludge is a relatively nonspecific indicator of potential gallbladder disease and appears to be related to neonatal stress from any source. Gallbladder wall thickening and sludge resulting from severe neonatal illness may be visualized by ultrasound study for several weeks despite pronounced clinical improvement. Identification of a normal gallbladder and biliary tract in a jaundiced patient is highly suggestive of the diagnosis of transient jaundice of the neonatal period or neonatal hepatitis. Failure to show the gallbladder and biliary tract on two separate examinations done when a patient is fasting is highly suggestive of biliary atresia, a finding that can be confirmed by technetium Tc 99m lidofenin (HIDA) radionuclide studies. A normal infant's common bile duct should measure 2 mm or less in diameter in the first three months of life. An internal

common bile duct measuring more than 2 mm in diameter suggests a pathologic or physiologic obstruction. Congenital hepatic tumors including hemangioblastomas and hepatoblastomas can be imaged sonographically. Benign vascular tumors of the liver including hemangioendotheliomas and mesenchymal hamartomas present as complex hepatic masses associated with dilated abdominal aortic and venous structures.

About 15% of neonatal abdominal masses arise from the gastrointestinal tract. These include omental and mesenteric cysts and gastrointestinal tract duplications. The hypoechoic concentric muscular thickening of pyloric stenosis is easily diagnosed by ultrasonography. Gastrointestinal masses can be distinguished from retroperitoneal masses and free intraperitoneal fluid due to peritonitis or hemorrhage can also be detected.

Many additional applications include the use of ultrasound to define normal neonatal genitalia and imaging pelvic masses in a newborn. One can also use ultrasonography to detect tethering of the neonatal spinal cord and to locate the level of the distal pouch in evaluating cases of imperforate anus. Diagnostic applications of rapid, noninvasive, high-frequency ultrasonography in neonatal abdomens continue to increase.

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Nuclear Magnetic Resonance Imaging of the Whole Body

IN THE PAST YEAR, the clinical evaluation of whole body nuclear magnetic resonance images has started at several centers in the United States. The technique measures the hydrogen density of a tissue and the effects of the molecular environment on the hydrogen. As a result, nuclear magnetic resonance provides cross-sectional images of the body with soft tissue contrast superior to that of x-ray computed tomography (CT). Spatial resolution is rapidly approaching that of CT and, in addition, there are no known hazards. Due to the static and varying magnetic fields and radio fields used, however, people with ferromagnetic or large metallic implants are presently excluded.

Because clinical evaluation has just begun, the actual clinical usefulness of whole body nuclear magnetic resonance imaging is unknown; it is showing good clinical potential in several areas. Because rapidly flowing blood causes blood vessels to be imaged as dark lumina, the vascular anatomy of the neck, mediastinum and abdomen can be seen in great detail without the need for intravenously given contrast agents. This effect of blood flow plus the ability of the nuclear magnetic resonance imager to be gated from a patient's electrocardiogram enables gated images of the heart to be obtained throughout the cardiac cycle.

Nuclear magnetic resonance clearly images all the major intra-abdominal, retroperitoneal and pelvic organs. It is presently comparable but not superior to CT in identifying most of the organs. Only a few pathologic conditions such as hepatic neoplasms have been studied in detail, but nuclear magnetic resonance imaging appears to have the potential to provide at least as much information as is obtained by CT.

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Ultrasonic Evaluation of Neonatal Vascular Catheters

THE ABDOMINAL AORTA and its branches, the inferior vena cava, portal vein and hepatic veins are readily imaged in the abdomen of a neonatal infant using high-frequency ultrasonography. Umbilical catheters are commonly used in neonatal intensive care. Ultrasound location of these catheters is a noninvasive technique that involves no ionizing radiation and has no known detrimental side effects. Sonographic catheter location allows direct visualization of the aortic bifurcation and renal arteries, thereby allowing one to assess the position of the catheter tip relative to the vessels. Coronal and decubitus scans in both transverse and longitudinal projections allow accurate locating of arterial and venous catheters and can detect intravascular thrombus associated with catheter placement. Locating catheters can also be done at crib side, which is particularly valuable in a fragile newborn.

Umbilical vessel anatomy determines the distinctive course of umbilical catheters seen on both plain film radiographs and by ultrasound. The arterial catheter passes through either of the periumbilical arteries, travels inferiorly towards the ipsilateral internal iliac artery, then turns cephalad and passes retrograde into the common iliac artery and from there into the abdominal aorta. In our nursery, optimal arterial catheter tip placement is below the origin of the renal arteries and above the aortic bifurcation; however, in some nurseries the catheter tip is placed in the midthoracic aorta. The umbilical vein catheter travels superiorly in the midline as the umbilical vein courses through the falciform liga-

ment to enter the liver where the umbilical vein joins the left portal vein. The catheter then crosses the portal vein to enter the ductus venosus and ascends through the ductus venosus to enter either the left or middle hepatic vein and from thence to enter the inferior vena cava on its way to the right atrium. Proper positioning of umbilical venous catheters should show the tip in the intrathoracic inferior vena cava or the right atrium.

About 17% of infants studied by the sonographic technique have had clinically evident signs of vascular compromise. Of these infants, ultrasound detected abnormal intravascular echoes or lack of radial pulsation in 10 of 12 or 83%. Abnormal echogenic foci, consistent with both thrombus and intimal dissections, were found. Ultrasonically detected abnormalities can be followed to resolution in infants. Typically the echogenic foci vanish and normal radial pulsation returns. The future evaluation of umbilical catheters within abdominal vessels can be augmented by combining Doppler analysis of flow within these vessels and high-frequency ultrasonic imaging. BARBARA A. CARROLL, MD

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Ultrasonographic Evaluation of Fetuses

BECAUSE OF technical improvements in both gray-scale and real-time ultrasound, prenatal ultrasonography has advanced far beyond its traditional roles of locating the placenta and determining fetal position, number and age. The fetus itself has come under increasing scrutiny. A variety of fetal anomalies can be consistently identified in utero. Recognition of many of these can dramatically alter patient management including the recent option of in utero interventional procedures.

The search for fetal anomalies with ultrasonography is carried out in two distinct patient groups. In the first group, the fetus is examined because of a genetic or familial history of a heritable disorder or an incidentally discovered risk factor such as an elevated amniotic fluid α-fetoprotein level. In these patients the prevalence of abnormality is high and an ultrasonographer knows which abnormalities may be present.

The second group includes those in whom a fetal abnormality is found serendipitously while the patient is being scanned for an obstetric indication, such as a discrepancy of size versus dates. In these patients the prevalence of anomalies is low. There is no genetic history of which abnormalities could conceivably be present. In such instances it is important not only to identify but to accurately characterize the lesion. For example, one should distinguish hydranencephaly from hydrocephaly; the prognostic implication is obvious. Accurately defined anomalies can alter the mode of delivery such as in cases of conjoined twins or a large sacral teratoma. The detection of such abnormalities as bilateral hydronephrosis, immune hydrops fetalis or hydrocephalus often affects the timing of delivery because such fetuses may be cared for more appropriately in a neonatal intensive care nursery than in their mother's womb. In addition, such lesions as posterior urethral valves and hydrocephalus can be diagnosed ultrasonographically and potentially treated in utero.

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Harrison MR, Golbus MS, Filly RA: Management of the fetus with a correctable congenital defect. JAMA 1981 Aug 14; 246:774-777

Percutaneous Drainage of Abdominal Fluid Collections

A LOCALIZED fluid collection in a critically ill patient who has a clinical diagnosis of abdominal abscess following a surgical procedure or an injury would have required surgical intervention in previous years, both for diagnosis and for drainage. Now in many instances these lesions may be percutaneously aspirated for a diagnosis and percutaneously drained for treatment by an interventional radiologist.

Locating a suspected intra-abdominal abscess is usually done by either sonography or computed tomography. These cross-sectional imaging techniques allow intraorgan, extraorgan and extra-alimentary fluid collections to be imaged both with precision and accuracy and in a rapid and noninvasive manner. Using these techniques, a safe percutaneous access to the fluid collection that avoids bowel, unaffected solid viscera and vessels can be planned. After finding the collection, an 18- or 20-gauge needle is placed in the fluid collection and a diagnostic aspirate is obtained. If the collection is unmistakably pus or infectious as noted by a Gram's stain, then a percutaneous catheter can be inserted to allow for continuous drainage. Appropriate antibiotics can be selected on the basis of results of a Gram's stain while results of cultures are pending. The catheter is connected to a closed-bag drainage system until drainage is completed. Noninfectious collections either may be aspirated through the needle or, if they are very large, a catheter may be inserted to allow for complete drainage over a one- to two-day period.

These drainage procedures are done using local

anesthesia and minimal premedication. They are well tolerated by patients. Patients avoid the risk of a major operation and anesthesia. Hospital stay, hospital costs and nursing care are reduced for these patients. Morbidity and recurrence of drained abscesses are less frequent than in those patients having surgical drainage.

All patients should have a surgical consultation because a complication or inadequate drainage may necessitate a surgical procedure. Contraindications include coagulation problems, an unsafe percutaneous route and some multiloculated collections that would require placing multiple catheters. Major complications include sepsis, enteric fistulas and laceration of blood vessels.

The therapeutic success rate of percutaneous abscess drainage has been as high as 90%. Percutaneous abscess drainage should be considered as a therapeutic approach when treating a patient with possible intra-abdominal abscess and radiographic evidence of intra-abdominal fluid collection.

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Needle Biopsy

RECENT ADVANCES in radiology, along with the technologic development of the "skinny" Chiba needle, have contributed to the current acceptance of the radiologically guided percutaneous needle biopsy. Cystic or solid lesions suspected of being malignant tumor, abscess or hematoma can be so diagnosed, thereby precluding the morbidity of an exploratory laparotomy. This procedure is particularly helpful when the likely diagnosis is a surgically noncurable malignancy or the patient is severely ill and a poor surgical candidate.

The Chiba needle is a 22-gauge thin-walled flexible steel needle with a 30-degree noncutting bevel and an inner fitted stylet. It and other needles similarly developed can generally yield enough aspirate for cytologic diagnosis.

Large lesions can be readily aspirated using either ultrasound (in the abdomen and pelvis) or fluoroscopy (in the chest). Smaller (2 cm or less) lesions or those near a vital organ can be reached with the guidance of computed tomography (CT). The three-dimensional aspects of ultrasound and CT enable the optimal path for needle placement to be selected, especially when the most direct path would involve passage through a vital organ. Computed measurement will indicate the desired depth of needle placement and angle of introduction.

As several specimens are often obtained, a second needle may be placed alongside the initially placed needle, using it as a guide. With this method reimaging of subsequent needle placements is often not necessary.

Aspirates obtained are immediately examined by an experienced cytologist—an absolutely vital step to this procedure. If samples are inadequate, the needle can be readjusted appropriately. "Failed" aspirates are often due to samples being taken from the necrotic center of a lesion.

Needle biopsy with the thin-walled flexible needles has proved to be a safe, quick and accurate method for defining the cause of chest, abdominal and pelvic masses. It may often obviate a surgical procedure and assist clinicians in an expedient manner in determining the most appropriate therapy.

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Sundaram M, Wolverson MK, Heiberg E, et al: Utility of CT-guided abdominal aspiration procedures. AJR 1982 Dec; 139:1111-1115

Vascular Occlusive Therapy

VESSELS CAN BE occluded for therapeutic purposes by using intravascular techniques. With these techniques angiographic catheter systems are used to deliver emboli or vasoconstrictors to the desired location. Among the situations that may be amenable to this form of treatment are arteriovenous malformations and fistulae, vascular tumors, vascular injuries, organ ablation and hemorrhaging.

Advantages of this type of therapy include decreased morbidity when compared with surgical alternatives and prompt application. At the time of initial diagnostic angiography, if a lesion is found it can be treated at the same sitting. In some cases the anatomic location of a lesion or a patient's clinical state makes surgical management impossible or unacceptably hazardous; vascular occlusion may be effective in such cases. It can also be used as an adjunct to surgical or medical care. Decreasing the vascularity of tumors or vascular malformations can make a surgical procedure easier in some cases. Hemorrhaging from unresectable tumors, the gastrointestinal tract and vascular injuries can be controlled.

A disadvantage of vascular occlusive therapy is that previous angiographic experience with catheter manipulations is necessary unless the vessels to be occluded are entered by direct surgical exposure. These techniques also carry more risk than routine angiography and risk versus benefit should be carefully weighed in

each case. In the hands of physicians who have committed themselves to mastering these techniques the complication rates are low.

Complications that can occur include unwanted infarction or ischemia of normal tissue, pain following the procedure—which is usually transient—and infection. Other complications are inherent risks in angiography, such as allergy to contrast agents, bleeding at the vascular access site and so on.

Many agents are used to induce occlusion. They can be grouped broadly into the following four categories: particulate emboli, mechanical devices, solidifying liquids and vasoconstrictor drugs. The particulate emboli include the most choices. The first decision to be made is whether a temporary or a permanent occlusion is desired. If temporary occlusion is desired resorbable surgical sponge particles such as Gelfoam may be sufficient. For permanent occlusion we have used polyvinyl alcohol foam particles or silastic beads. When larger vessels are to be occluded a mechanical device may be necessary. This includes inflatable and detachable balloons and metal spring or coil devices such as the Gianturco coil. Most of the balloon catheter systems and solidifying liquids are still investigational. The vasoconstrictor drug used most often is vasopressin and it is used primarily for the control of gastrointestinal bleeding.

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Interventional Biliary Radiology

DURING THE PAST DECADE significant advances have been made in radiologic procedures involving the biliary tract. In 1973 Burhenne described nonoperative removal of retained gallstones from the common bile duct. This is now the procedure of choice for removing postoperatively retained stones. Extracting retained stones is easier in relatively thin patients, when the drainage tract is short and straight and when the T tube is large, preferably Nos. 14 to 16 French.

Following cholecystectomy and T-tube placement, four to six weeks are allowed to pass for development of the T-tube tract. T-tube cholangiography is again done to confirm the presence and determine the location and number of stones. The T tube is removed and a steerable catheter is promptly inserted in the T-tube tract. Fluoroscopy is used for guidance. The stone-retrieval basket is placed through the larger caliber steerable catheter and the stone is engaged in the basket and then extracted. Single or multiple stones can be removed in this fashion. If stones are too large to be removed via the T-tube tract, they can be broken into smaller, more easily extractable fragments and sometimes even flushed into the duodenum.

Some authors, such as Katzen, recommend that patients be given a broad-spectrum antibiotic such as ampicillin, 1 gram by mouth four times a day, one day before and until two to three days following the procedure, if done on an outpatient basis.

Percutaneous transhepatic cholangiography is now a well-established procedure for delineating the anatomy of the biliary tree in patients who have suspected biliary obstruction. Percutaneous decompression of the biliary system by means of a special catheter is an extension of the diagnostic percutaneous cholangiogram. This is done by placing a sheathed needle into the liver and positioning the tip into a dilated biliary radical. This catheter is placed in the biliary tree under fluoroscopic guidance while contrast material from the diagnostic cholangiogram is still in the biliary tree. A guide wire is inserted through the sheath and advanced beyond the site of obstruction. By manipulating the guide wire it can usually be made to traverse the obstruction. A specially designed Ring or pigtail catheter is then placed over the wire so that its tip lies in the duodenum. The pigtail shape serves to anchor the catheter in the duodenum and to minimize the risk of inadvertent removal. The bile enters side holes in the portion of the catheter above the obstruction and can flow through the catheter into the duodenum.

Considerable reduction in serum bilirubin level is effected in most patients. Biliary stent placement can help relieve pruritus caused by pronounced hyperbilirubinemia. Biliary decompression can also help reduce the risk of infection present in an obstructed biliary system. Biliary stent placement may effect palliation, without surgical intervention, for patients suffering from inoperable carcinoma of the pancreas or biliary tract.

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Digital Subtraction Angiography

DIGITAL SUBTRACTION ANGIOGRAPHY couples a digital computer to a conventional x-ray fluoroscope to augment the visualization of blood vessels, using standard radiographic contrast media. Whereas it has been used in conjunction with selective catheter arteriography for enhanced visualization of vascular and neoplastic lesions, the enthusiasm for this procedure results from

its ability, by means of intravenously given contrast agents, to visualize lesions in blood vessels.

Digital subtraction angiography requires the intravenous delivery of 20 to 40 ml of contrast agent over one to three seconds. This rapid delivery of contrast agent requires the placement of a 16-gauge needle in the antecubital vein, or passing a small No. 5 French catheter percutaneously from the antecubital or femoral vein into the superior or inferior vena cava. With these venous injections, some method of computer enhancement of the x-ray images is required to render the arterial structures visible. Typically a subtraction scheme is used—that is, images obtained before the injection of contrast are subtracted from those obtained after the injection of contrast. This *temporal subtraction* gives excellent visualization of extracranial carotid arteries, thoracic and abdominal aorta, renal arteries and peripheral vascular arteries. An important requirement for this temporal subtraction to be effective is that there be no voluntary or involuntary subject motion between the preinjection and postinjection images. In about 20% of the patients, the motion effects are disturbing enough that the information obtained is incomplete. Other situations producing inadequate digital subtraction angiography studies include poor cardiac output, inadequate venous access or inability to define a lesion exactly due to the problems of superimposition of other blood vessels. Overall, this examination technique is successful in 70% to 80% of patients. A number of correlative studies comparing it with standard catheter arteriography have shown that for the extracranial carotid, aorta, renal and peripheral arteries, a technically satisfactory digital subtraction angiography examination provides acceptable diagnostic information.

This technique has been extensively evaluated clinically at a number of centers. It has found a role in the evaluation of extracranial carotid occlusive disease, screening of asymptomatic carotid bruits, evaluation and detection of renal vascular hypertension, evaluation of bypass graft patency and detection and evaluation of thoracic and abdominal aneurysms. Its use for pulmonary arteriography is somewhat controversial. The examination is definitely useful, however, for showing major central pulmonary emboli, but its role in detecting more peripheral emboli is uncertain. It has also been used satisfactorily in children. For cardiac applications, it has been used for evaluating left ventricular function. The results of using it for detecting coronary artery bypass graft patency have not been particularly rewarding, and for coronary arteriography it remains an important, but as yet unreached, goal.

Digital subtraction angiography is an invasive examination. Its appeal relates to the opportunity for outpatient arteriography, reduced patient risk by eliminating selective arterial catheterization and improved patient comfort. Much of the discomfort that occurs through the injection of contrast media selectively in arteries is reduced or eliminated through the intravenous route.

On the other hand, substantial amounts of contrast media are used for the digital subtraction angiography examination and the direct systemic effects, as well as the potential allergic effects of the use of the media, must be balanced against the clinical indications for the examination.

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High-Resolution Computed Tomography of the Temporal Bones

THE HIGH SPATIAL RESOLUTION of computed tomography (CT), particularly with sectional or target imaging, is ideal for evaluating the temporal bones. A preliminary digital radiograph is taken and by using a cursor for locating, a series of thin (1.0 to 2.0 mm) scans is taken through the petrous temporal bones. The horizontal or axial plane is usually used. When possible, direct coronal scans can also be done with a patient's head hyperextended in the supine or prone positions. Target bone reconstruction is used for maximum spatial resolution to enhance bony detail.

Traumatic hemorrhage into the air-containing cavities of the temporal bone is recognized better by CT than by conventional pleuridirectional tomography. Opacification with or without fluid levels is discernible within the mastoid air cells or tympanic cavity.

The common tympanolabyrinthine or purely labyrinthine fractures of the temporal bone are vertical plane fractures. Axial CT sections are ideal for evaluating vertical fractures. The supine position is comfortable for a patient and the procedure can be done in emergency situations, even with polytraumatized patients. The CT examination can also provide information on traumatic lesions of the temporomandibular joint, the mandibular condyle or the base of the skull.

In patients with chronic otitis media, CT will show bony modifications such as bony sclerosis, hypopneumatization of the air cells or bony erosion. Demineralization or osteitic erosion of the ossicles, with or without displacement of the ossicles, may be detected in cases of cholesteatoma. CT in the axial plane is the best way to show a labyrinthine fistula of the lateral semicircular canal, which may be difficult to diagnose by conventional pleuridirectional tomography. Because of its superior density resolution, CT is useful in evaluat-

ing postoperative cholesteatomas when traditional tomographic landmarks such as the attic wall have been removed.

Thin-section CT is used to evaluate modifications of the cochlea in patients with labyrinthine otosclerosis. In addition, the scanner can be used to locate materials used in ossiculoplasties such as a stapes prosthesis.

Agenesis or hypoplasia of the external auditory canal or malformations of the tympanic cavity and ossicles can be shown by computed tomography. For inner ear malformations, axial CT is ideal for evaluating the cochlea when searching for a Mondini malformation. Complex malformations can be similarly studied to document dilatation of the vestibular aqueduct, the semicircular canals or the vestibule. The addition of intrathecal metrizamide with CT cisternography may help to show a fistula or a dehiscence of the fundus of the internal auditory canal in patients who have recurrent episodes of meningitis with cerebrospinal fluid otorrhea.

When tumors of the ear or temporal bone are suspected, CT should be done before and after intravenous injections of contrast material. CT, with its superior soft tissue detail, can more accurately determine the extent of disease in comparison to previous radiographic techniques such as plain films, pleuridirectional tomography and vascular studies. Not only is CT a significantly improved method of assessing the extent of these tumors preoperatively, but it is also useful in detecting tumor recurrence.

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The Role of Computed Tomography for Evaluating Temporomandibular Joints

HIGH-RESOLUTION x-ray computed tomography (CT) is a useful new radiographic method for evaluating the temporomandibular joints. For most exquisite detail, thin-section (1 to 2 mm) axial dynamic scanning with maximum milliampere seconds and 0.5 to 1 mm overlapping is done so that motion-free, vertically reformatted images may be made. It is helpful to reconstruct images with both soft tissue and bone detail algorithms.

When we studied more than 50 patients, the method was particularly useful in two categories of patients: those with chronic joint pain and dysfunction and those suffering head and facial trauma. As in the case of the intervertebral disc, the fibrocartilaginous temporomandibular joint meniscus may be visualized when dislocated. If the meniscus is macerated, the joint space may be severely narrowed. The accuracy of computed tomography for directly visualizing dislocated meniscus is about 80% in our experience.

Often unexpected injuries accompany facial and head trauma. CT has been particularly useful in discovering temporal fractures that extend onto the temporomandibular joint articular surface, for follow-up of cases of condylar and neck fractures and for problems of reduced opening, as with bony and soft tissue ankyloses.

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Nuclear Magnetic Resonance Imaging of the Central Nervous System

THE POTENTIAL of nuclear magnetic resonance imaging of the central nervous system has been reported in many recent articles. The rapid development of this technology, however, has resulted in confusion concerning its clinical applications for evaluating neurologic alterations. Definition of its future role is further complicated by the lack of standardization of both the imaging hardware and the techniques of signal acquisition. Preliminary experience suggests that the technique is superior to computed tomography (CT) in detecting some disease processes and complementary to CT for evaluating others.

The sensitivity of nuclear magnetic resonance imaging to alterations in tissue characteristics is most evident for multiple sclerosis. The lesions of multiple sclerosis are shown as high-intensity foci with spin echo techniques. Inversion recovery images depict the lesions as areas of low signal intensity. Nuclear magnetic resonance spin echo images defined all of the lesions seen on the corresponding CT scans and many more that were not evident on CT.

This type of imaging may be done in the sagittal and coronal planes directly, in addition to the conventional axial tomographic plane. The soft tissue contrast realized is superior to CT, and in addition there is the notable absence of beam-hardening artifacts due to bone. These factors make this imaging technique ideally suited for evaluating the posterior fossa and also the spinal cord, where pathologic alterations such as tumors or syrinx cavities may be shown without intrathecal contrast.

Areas of infarction are defined by both CT and nuclear magnetic resonance; the latter modality, however, shows more extensive tissue involvement in both acute and subacute lesions. The characterization of an

infarct as ischemic or hemorrhagic is facilitated by calculating nuclear magnetic resonance relaxation times.

Tumors are seen with both CT and nuclear magnetic resonance, but the latter is more sensitive because it has superior contrast resolution. In addition, it requires neither ionizing radiation nor iodinated contrast material to detect pathologic alterations. The potential characterization of tumors by their tissue relaxation times will require additional clinical experience and research.

Vascular anatomy is exquisitely defined by nuclear magnetic resonance images without contrast agents. Variations of the signal intensity of flowing blood are produced by alterations of the instrument parameters. The technique's ability to quantify blood flow is currently under extensive investigation.

The full potential of nuclear magnetic resonance as imaging technique has yet to be elucidated. However, the superiority of this new technique to CT in delineating some pathologic alterations of the central nervous system is already apparent. CATHERINE M. MILLS, MD

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Radiotherapy for Prostatic Carcinoma

HIGH-DOSE IONIZING RADIATION is effective in controlling and potentially curing localized carcinoma of the prostate. In addition, irradiation can provide excellent palliation of symptoms in advanced disease. Programs currently using irradiation for treating early adenocarcinoma of the prostate gland can be divided into the following three basic plans, as outlined under stages B and C_1 (the advantage of one treatment plan over the others has not been established):

Stages B and C_1

1. External-beam radiation only.
2. Pelvic lymphadenectomy combined with radioisotope implant.
3. Pelvic lymphadenectomy, radioisotope implant and external-beam radiation.

A fourth treatment option that does not include irradiation is prostatectomy, which is usually limited to patients with small, low-grade lesions not involving the capsule and confined to one lobe of the prostate.

Stage A_2

All of the treatment options noted for stages B and C are used, although radioisotope implants are less frequently done.

Stage A_1

All of the treatment options noted above have been used as well as others. Close observation only is often suggested for patients having favorable prognostic factors.

Selecting the appropriate treatment is a multidisciplinary task for a team of oncologically trained and experienced physicians representing each modality involved in a patient's evaluation and therapy. Treatment planning must include consideration of major prognostic factors—that is, the extent of the primary lesion, the histologic grade (Gleason's score) and the extent of lymph node involvement. The patient's own desires must also be considered.

The external-beam option has been described by Bagshaw, who reported the results of using external-beam radiation for the treatment of 351 patients at Stanford University (Stanford, California) who had tumors confined to the prostate (nominal stage B or T_1). The actuarial survival rate was 78% at 5 years, 57% at 10 years and 39% at 15 years. In the same study, 310 patients with extracapsular extension (nominal stage C or T_2 and T_3) were noted to have an actuarial survival rate of 59% at 5 years, 39.5% at 10 years and 30% at 15 years. Patients treated before 1973 received radiation to the region of the prostate only, and after 1973 patients believed to be at significant risk for lymph node metastasis received radiation to extended fields encompassing the pelvic nodes.

Relating to the second treatment option, Grossman and co-workers published their analysis of the first 100 patients at Memorial Sloan-Kettering Cancer Center (New York, New York) with stages B and C disease treated by means of bilateral pelvic lymphadenectomy and retropubic implantation of iodine 125 seeds. For 53 patients having disease limited to the prostate (stage B_1, B_2 or B_3), the five-year crude survival rate was 89%; the five-year disease-free survival rate was 60%. The early stage B lesion—that is, tumor confined to one lobe of the prostate gland—resulted in a 95% five-year crude survival rate and a 67% five-year disease-free survival rate. In all, 34 patients with extracapsular extension (stages C_1, C_2 or C_3) undergoing similar treatment were reported to have a five-year survival rate of 79% and a disease-free interval of 23%.

Guerriero and colleagues from Baylor College of Medicine (Houston, Texas) reported their results with the combined use of lymphadenectomy, interstitial implants using gold 198 seeds and external-beam radiation, which represents the third treatment option. The five- to ten-year crude survival rate for 33 stage B patients was 91%; the disease-free rate was 52%. In all, 20 stage C_1 patients were reported to have an 80% five- to ten-year crude survival rate and a 65% disease-free rate.

Severe irradiation complications are generally reported to involve less than 5% of patients and are usually limited to proctitis, cystitis, urethral stricture, rectal stenosis and, rarely, small bowel obstruction.

Impotence following irradiation is reported to occur in from 2% to 30% of patients, suggesting in part the inherent difficulty in obtaining information regarding this problem.

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Percutaneous Transluminal Angioplasty in Peripheral Vascular Disease

THE DILATING BALLOON CATHETER developed by Grüntzig in 1976 greatly expanded the role of percutaneous transluminal angioplasty in the management of peripheral vascular disease. Unlike the coaxial dilating catheters originally introduced by Dotter and Jenkins in 1964, balloon catheters are flexible enough to allow dilatation of branch vessels and vessels at a great distance from the puncture site. In addition, balloons allow dilatation of stenotic lesions in large vessels, such as the iliac arteries, to a considerably larger luminal diameter. When compared with surgical treatment of peripheral occlusive disease, balloon catheter angioplasty is less expensive, less uncomfortable and has a lower risk and a much shorter convalescence. Treatment can be easily repeated, if needed, because access to the lesion is not impaired by postoperative scarring. Percutaneous transluminal angioplasty can be used safely in patients for whom a surgical procedure would carry a prohibitively high risk. Finally, if the procedure is unsuccessful, it rarely complicates or alters a subsequent surgical procedure. These advantages have led to a rapid growth in the use of percutaneous angioplasty: Dotter estimates that as many as 30,000 were done in the United States during the past year.

Several series have reported successful application of the technique in the treatment of iliac and femoral occlusive disease. Our initial success rates for iliac dilatation have been about 95% and three-year patency rates about 80%. Three-year patency rates for iliac lesions less than 2 cm in length have been about 86%, which is comparable to those of aortofemoral bypass grafting. Initial success rates for femoral-popliteal dilatation have been about 85% and three-year patency rates about 70%. Three-year patency rates for femoral-popliteal lesions less than 8 cm in length have been about 83%, which is comparable to the best results reported for femoral-popliteal bypass grafting using autogenous vein grafts and higher than those reported using synthetic grafts. Intimal hyperplasia developing within venous bypass grafts and at surgical anastomoses has proved responsive to percutaneous dilatation, and percutaneous transluminal angioplasty has prolonged the patency of the bypass grafts in this setting. The death rate directly attributable to this procedure has been about 0.4%, very much less than the 4% average mortality reported for femoral-popliteal surgical procedures. The morbidity rate has been about 5%, including hematoma (1%), clinically significant embolization (1%) and vessel thrombosis following dilatation (3%). The last rarely affects later surgical management.

When choosing the proper therapy for an individual patient, one should take into account the location, appearance and natural history of the lesions, the state of health and age of the patient and the severity of symptoms. This requires that an angiographer have a thorough clinical knowledge of peripheral vascular disease, including the limitations and hazards of each therapeutic option, as well as its proper application and chances for success. Great expertise in angiographic technique may be needed for safe passage of catheters through diseased or completely occluded arteries. Complete cooperation between radiologists and vascular surgeons is imperative if patients are to receive the best possible care. When these conditions are met, percutaneous transluminal angioplasty can be a useful tool in the treatment of many patients with obstructive peripheral vascular disease.

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Percutaneous Catheter Drainage of Abscesses

ADVANCES IN ULTRASONOGRAPHY, computed tomography (CT) and the radiologic understanding of abdominal anatomy, coupled with catheter techniques, have significantly altered the current approach to intra-abdominal abscesses. Immediate detection by cross-sectional imaging, diagnostic aspiration with fine, 22-gauge needles and subsequent percutaneous placement of drainage catheters is now well accepted and often the preferred therapy. The expanded role of an interventional radiologist in day-to-day ward care of patients is a concomitant outgrowth of the procedure.

Numerous studies have ascertained the prominent role of ultrasound and especially CT for accurately detecting abscesses. Under guidance by these techniques, aspiration and immediate Gram's stain establish the diagnosis of abscess and allow the institution of appropriate antibiotics. Candidates for percutaneous abscess drainage most frequently have pyogenic abscesses. Those with "sterile" abscesses (patients receiving antibiotics on a long-term basis), infected necrotic tumors, large amebic abscesses, hematomas and bile collections are all treated by similar techniques; the duration of

catheter drainage is usually shorter, however. Puncture of a suspected *Echinococcus* cyst is always avoided.

The most important aspect of percutaneous abscess drainage is determining a safe entry route. Abscesses abutting the parietal peritoneum have the easiest access. If computed tomography shows an unobstructed pathway to the abscess, deeper collections may be drained. Overlying viscera, bowel, large vessels and sterile cavities are avoided in placing the catheter. The idea is not to harm other structures or spread infection. Interloop abscesses and those in the pancreatic head region are the most difficult to reach.

The technique of percutaneous abscess drainage involves direct trocar insertion or guide-wire exchange (Seldinger technique). The catheter may be placed under computed tomography, ultrasound, at fluoroscopy or by a combination of these. Abscess morphology, operator preference, modality availability and time constraints govern these decisions. In the evolution of percutaneous abscess drainage, a host of catheters has been used. Recently, specifically designed catheters with large holes, sump designs and facilitated insertion devices have become popular.

Catheter aftercare often determines the outcome of the procedure. As with surgical therapy, irrigation is a major component. Sequential sinograms are the usual mode of follow-up and record cavity shrinkage and obliteration. Patients responding poorly will have follow-up computed tomography or ultrasound and sinography to search for synchronous abscesses, loculations or fistulae.

Results of percutaneous abscess drainage support its prominent role as an alternative to surgical therapy and often as the procedure of choice. A complete cure with avoidance of laparotomy and general anesthesia has been reported in 75% to 95%. When treatment failures occur, patients may still undergo operation. For critically ill patients, a temporizing percutaneous drainage makes them more fit for a surgical procedure. Complications occur in 5% to 10% of patients. Recurrences indicate an underlying abnormal communication, such as an enteric fistula, anastomotic leak or pancreatic duct communication.

No controlled study comparing surgical and percutaneous drainage has yet been done. Inherent differences and problems for this type of study involve selectivity of cases in drainage; many patients undergoing percutaneous abscess drainage, however, are frequently quite debilitated and critical.

New procedures as outgrowths of percutaneous abscess drainage are developing. These include percutaneous drainage of loculated empyemas after failure of chest tube therapy, pancreatic pseudocyst drainage, pericardial drainage and percutaneous cholecystostomy. Tried and proved surgical dicta are adhered to whenever possible, as with conventional percutaneous abscess drainage. Early results are promising, but await further experience.

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Neurosonography in the Operating Room

IN THE PAST, neurosurgeons have had many complicated procedures with which to identify the nature and position of an intracranial pathologic condition, which include angiography, computed tomography and nuclear medicine. Even with these sophisticated techniques, however, at the time of a surgical procedure after the surgically created cranial defects have been made, the dura reflected and the cortex of the brain exposed, the neurosurgeons have had to rely on their expertise and experience to define where to proceed in a dissection. They have not had a tool at the time of the surgical procedure to locate an intracranial lesion. Ultrasonography now enables them to actually define an intracranial lesion intraoperatively; to characterize it as solid, cystic or complex; to determine its size and location from the surface and its relationship to adjacent anatomy, and to detect pulsatility. This information is gained almost instantaneously when the transducer is gently placed on the cortical surface. Most pathologic lesions are discrete and clearly distinguishable from adjacent brain tissue and are easily recognized even by those who are inexperienced in ultrasonic techniques.

The depth of the dissection in relation to the pathologic lesion can be defined by filling the dissected area with saline and placing a surgical sponge within the innermost recesses. These surgical sponges are extremely hyperechoic and serve as excellent markers for the depth of the dissection. By ultrasonography one can determine precisely where to take the biopsy specimen or where to resect and can assess thereafter how much residual tumor has been left behind or, on the other hand, whether or not all the tumor has been removed. Ultrasound studies also detect as a bright hyperechoic interface a cannula or needle introduced for location and its relationship to the lesion, as well as the position of ventricular shunts.

The ultrasonic industry is in ferment in developing the ideal intraoperative unit. At present, sector real-time scanning seems to be the most appropriate tool. The unit we are using is a neurosector machine (developed by the ATL Corporation) that has a conical transducer. It is a mechanical sector scanner that produces pie-shaped images instantly in any plane. For use in the operating room, sterile gel is applied to the conical surface of the transducer and thereafter a sterile sheath encases the transducer and the cord. Sterile rubber bands stabilize the sheath. The machine itself has a flat surface; a sterile plastic is placed upon

the face of the unit so that the operator can manually touch and manipulate the machine and the tape recorder without breaking sterile technique. The transducer frequency can be changed with a touch of the finger from 3 to 5 or 7.5 MHz. The 3-MHz transducer produces an image across the surface of the brain from one cortical surface to the opposite side. The 5-MHz transducer has a greater resolution but the depth is limited to the midline whereas a transducer of 7.5-MHz frequency produces the highest resolution but has a focal point depth of only 2 cm from the surface. Therefore, this transducer is reserved for superficial lesions. Sterile saline is an effective coupling agent between the transducer and the brain surface.

Because ultrasound does not cause any known biologic harm at the energies used in diagnosis, it is a safe tool to use on the delicate tissue of the brain. Early experience suggests that this technique is appropriate and extremely useful in locating a wide spectrum of intracranial lesions—including neoplasms and infections—and in placing ventricular shunts.

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Editorials

A New Clinical Investigation Section

WITH THIS ISSUE the *WJM* inaugurates a Clinical Investigation Section in affiliation with five western societies that are interested in clinical research. This section should be of particular value to those readers who are students or residents, or themselves do research. However, it is expected that each article will contain something of clinical or potential clinical interest and so should be worth the attention of virtually all of our readers. We look forward to the development of this section under the leadership of R. Paul Robertson, MD.

—THE EDITORS

Some Elements of Quality

IN THESE TROUBLED TIMES when there is so much emphasis on trying to make health care less costly or, as some might say, cheaper, physicians and the medical profession have quite properly taken the stand that while cost control is a worthy goal to be vigorously pursued, this must not be at the expense of the quality of care that is available to our patients and to the public. While it is clear the cost and quality of patient care have some relationship, it is also a fact that the costs are comparatively easy to measure whereas it has not been so easy to define or measure the quality. For this reason it is often difficult to show in what ways quality is or is not sacrificed when costs are cut. There is a pressing need to know more precisely what we are talking about when we speak of quality in patient care.

It is generally conceded that the Japanese automobile makers have found ways to make automobiles of better quality at less cost than have American manufacturers. Given the many reasons for their lower costs (some of which are obvious and some probably not so obvious), one may then ask how they make sure of the quality of their product. It has been said that the Japanese automobile makers have identified four elements that should be present in the manufacturing process to assure quality. These are (1) standards, (2) performance, (3) accountability and (4) something that might be called esprit de corps or a sense of group pride in the quality of the product. Apocryphal as this may be, perhaps something can be learned from it about how to tell better whether quality is or is not present in patient care as this is rendered under one or another economic arrangement.

Standards. We have already in place a relatively sophisticated system of standards for professional education (accreditation and certification), for drugs and equipment (FDA) and for hospitals and health care institutions (JCAH and licensure). We are beginning to develop generally accepted standards for the therapy of some conditions such as hypertension and diabetes mellitus. As the scientific data bases improve it may be expected that there will be more accepted standards for the treatment of more conditions. So it is indeed true that the medical profession has its standards and that they are high. It is only to be hoped that they will not be too seriously eroded by antitrust or other shortsighted actions by governments, courts or anyone else.

Performance. Over the years the medical profession has been increasingly concerned about performance in patient care. It began with tissue committees in hospitals which sought to relate surgical procedures to outcomes. More recently other forms of peer review have become commonplace, especially in hospital settings. The harsh realities of successful malpractice actions, both justified and not so justified, have focused greater attention on practice performance. So far it has been difficult to apply peer review to practice performance in physicians' offices outside of a hospital, clinic or a group practice. While the medical profession has been a leader among the professions in developing peer review of practice performance, its monitoring of professional performance certainly does not match the monitoring of the performance of the workers that is done to assure quality in a Japanese automobile. We are probably only at the beginning of what needs to be done in peer review of practice performance by physicians and other health professionals if we are to be able to measure and assure the quality of care rendered in the different economic arrangements that are coming into being.

Accountability. Accountability is a step beyond actual performance. It requires data to support what is done. To the extent that medical practice is an art this accountability is difficult; to the extent that it is a science data can be developed so as to make it accountable. The science of accountability in medical practice and patient care is in its infancy, yet it seems essential that this be developed if we are to know whether or not there is quality in patient care rendered in different settings.

Esprit. Esprit is something more readily sensed than measured. One senses that it is now usually present in good measure among health care providers, in health care institutions and in the health care teams that give care to patients. But one also senses that this esprit may be fragile and become threatened in circumstances where harsh competition displaces an atmosphere of cooperation and close collaboration, or when unwanted or poorly understood policy decisions are made by far-off governments or some sort of absentee corporate landlords. Although difficult to measure, esprit or pride in workmanship among physicians and other health care providers is an essential element in the quality of patient care.

At this moment the powers that be in government and elsewhere are giving lip service to maintaining quality

while trying desperately to reduce costs in health care. Perhaps this is all that can be expected until exactly what is meant by quality becomes more tangible and more visible for all to see. Clearly this urgently needs more attention by the medical profession. There just might be a lesson to be learned from the apocryphal Japanese automakers' attention to standards, performance, accountability and esprit among workers to assure quality in spite of lower costs. —MSMW

Chemicals and the Development of Cancer

In the past two decades a radical change in the perception of cancer by the medical profession and by the public at large has occurred. From a disease almost universally viewed as being of unknown origin or causation some three decades ago, cancer has become perceived today as *the* ultimate expression of environmental contamination. This extreme view is very widely held but is perhaps only partially valid.

As clearly stated by Smuckler in this issue and in other recent reviews,[1-4] many epidemiologic studies, backed by an increasing body of experimental work, have implicated a variety of chemicals (some 30-odd), some viruses and several forms of irradiation, as initiating causes of human cancer. Many cancers of the respiratory tract and some of the genitourinary system, upper gastrointestinal tract, skin and thyroid have environmental components, often chemicals, as important etiologic agents. This has naturally led to the popular thesis that a major advance in cancer prevention will rapidly occur when the offending environmental agents are identified and removed. This is no doubt true in some instances—for instance, smoking and lung cancer, certain chemicals and bladder cancer, vinyl chloride and thorotrast and angiosarcoma of the liver, asbestos and mesothelioma—to name some of the more obvious examples. The exposures to the chemicals in these instances are often intensive or prolonged, or both.

Yet research in the past decade or so has been toward a major modification of this viewpoint, namely that *exposure* to a carcinogen is by no means synonymous with induction of cancer and that the presence of the carcinogen in the environment is but one factor in a multifactorial matrix or network. Although we now appreciate more readily the complex multistep nature of the very long "preneoplastic" or "precancerous" stages in cancer development with chemicals and other agents, evidently even for the very early steps of initiation, such a perspective is more realistic and valid than is the previous simple equation of exposure and risk.

There are at least five interacting segments of a network that determine what effect a certain exposure to a carcinogen might have on initiating the carcinogenic process: (1) concentration and duration of exposure to the carcinogens; (2) the efficiency with which a chemical is metabolized to an active carcinogen or to noncarcinogenic derivatives; (3) the efficiency with which the target tissue cells are able to "detoxify" carcinogens; (4) the presence and rate of repair of chemical and physical damage to DNA,[2] and (5) the presence or induction of cell proliferation in target cells.

1. A clear-cut dose response is seen in many instances with chemical carcinogens in humans. For example, with smoking and with occupational exposure to aromatic amines (benzidine, β-naphthylamine), vinyl chloride and the like, a relationship between levels of exposure, duration of exposure and cancer incidence has been documented. With the large number of carcinogens that are found in our environment, however, the dose range is often quite low. Under such circumstances, the other four known factors almost certainly play a determinant role.

2. The metabolic capability for different carcinogens (or, more accurately, "procarcinogens") varies enormously from tissue to tissue and species to species. In general, humans are quite capable of metabolizing many procarcinogens of different types to active carcinogenic derivatives.[1,2] The variations in this capacity are no doubt an important factor in determining the organ sites for different carcinogens.

This component of the network is modulated by diet, hormones and genetics. Major positive or negative influences on metabolic activation can be shown for each of these three major types of modulators in animals. Conceivably, the known effects of diet, hormones and genetics on human cancer incidence may be exerted in part on this aspect of carcinogenesis.

3. A factor that is now receiving increasing attention is the efficiency with which cells or tissue can "soak up" or inactivate activated forms of carcinogens. Glutathione and the enzymes glutathione-S-transferase, epoxide hydrolase and glucuronyl transferase, among others, are able to convert active carcinogens to various conjugated forms or to hydrated forms, steps that lead either directly or indirectly to inactivation.[5] Each tissue has a constellation of enzymes and other components that can readily inactivate active derivatives of potential carcinogens, mutagens and other xenobiotics. Such reactions have been shown to protect cells against damage to DNA and other macromolecules by carcinogens.

4. The efficiency by which damage to DNA is repaired is a critical factor in the genesis of epidermoid carcinoma and melanoma by ultraviolet light in humans (for example, xeroderma pigmentosum). Conceivably the same might also be operating for chemical carcinogens, because virtually every tissue has a spectrum of "repair enzymes." The exact role of such repair activity in the genesis of cancer by chemicals in humans has yet to be delineated.

5. Cell proliferation is known to be an essential step in the initiation of carcinogenesis with chemicals and probably also with some viruses and radiations. In the liver, pancreas, urinary bladder and other adult "quiescent" tissues, there is good evidence that local tissue damage (such as toxic hepatitis) plays an essential role in starting the carcinogenic process. The tissue damage leads to local cell proliferation and the latter is required

before a chemical can initiate the carcinogenic process in such tissues.

This might well be an important factor in the very high incidence of liver cancer in many countries in Asia and Africa. Although a close association with exposure to hepatitis B virus is now widely appreciated, there is good evidence that liver cell damage may be quite important. Thus, cellular injury induced by any agent or associated with other diseases such as liver cirrhosis, chronic pancreatitis or chronic cystitis might well play important roles in facilitating the initiation of cancer development in the organs or tissues in which normal cell proliferation is minimal or absent.

This shows the type of interplay between known factors that probably plays a role in determining the susceptibility of persons to the carcinogenic consequences of exposure to chemical carcinogens. A similar delineation of important modulating factors might become possible for later steps in the carcinogenic process, such as those associated with promotion and progression. As physicians, the challenge lies in identifying those specific factors that modulate against initiation or subsequent steps in the development of cancer. Their study could well have a major influence in devising a rational and acceptable way to prevent some forms of cancer.

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The Social Transformation of American Medicine

The Social Transformation of American Medicine,[1] a book written by Paul Starr, an Associate Professor of Sociology at Harvard University, should be read and reflected upon by any physician who is in a position of leadership in our profession in these unsettled days, and by any physician who wishes to know more about how we as a profession have got to where we are. The work is superbly documented and it rings true to one who has been more than casually concerned with developments in medicine and health care over the last quarter century. It is not hostile to medicine. It gives organized medicine its due, but suggests that forces beyond the control of medicine or anyone else have done the most to shape what Starr calls a "sovereign profession" and are now bringing about its "social transformation" into something that yet remains to be seen.

He notes that as medical care has become something worth having and as it has become more costly—it has become "everybody's business" as is evidenced by three "revelations" of the 1970s. The first was a discovery of a "health care crisis" by the liberals which was to open the way for governmental reform of what was touted to be a "new system" of health care. As costs continued to rise, there was a second "revelation": Health care was found hardly to improve health at all and in fact might even be harmful to it. This made the first revelation seem less important and diverted attention to cost control. And the third "revelation," this time espoused by conservatives, revealed that the problems of health care in America could be solved by relying on competition and incentives, if the government's role were reduced to a minimum. At present Starr believes that no group is dominant and that there is no evidence that one approach is better than another. He does suggest that doctors continue to hold a strategic position through their established relationships with patients and hospitals, as they enter the emerging world of zero-sum medical practice and as the new medical corporations hove upon the scene.

While this book offers no clear vision of what the future will be, it does provide insight into the forces that have brought us to our present situation and which may help to shape the further evolution, and likely the transformation, of medical practice and patient care in this nation. It should be required reading for those most concerned with and about these problems. MSMW

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Case Reports

Central Nervous System and Genitourinary Blastomycosis: Confusion With Tuberculosis

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INFECTION WITH the dimorphic fungus *Blastomyces dermatitidis* causes a wide spectrum of disease, ranging from asymptomatic pulmonary infection to a fatal systemic illness. Although effective antifungal therapy is available, the difficulty in establishing an early diagnosis hampers management of the disease.

We describe a fatal case of blastomycosis occurring in a nonendemic area that illustrates the difficulties in distinguishing blastomycosis from tuberculosis. Furthermore, this report shows the importance of carefully searching for evidence of blastomycosis elsewhere than the central nervous system when there is unexplained chronic meningitis. In addition, blastomycosis as a cause of hypothalamic-pituitary dysfunction, as described in this case, has only infrequently been reported.[1]

Report of a Case

The patient, a 54-year-old heavy equipment operator, first presented to the Portland Veterans Administration Medical Center on August 10, 1981, because of urinary frequency and hesitancy. On examination he had a tender prostate and analysis of urine showed 20 leukocytes per high power field without visible bacteria. Empiric treatment with trimethoprim-sulfamethoxazole resulted in symptomatic improvement. Culture of a urine specimen obtained before therapy was negative for bacteria.

First Admission, September 1, 1981

Three weeks later he was admitted to hospital because of shortness of breath, cough, night sweats, polyuria, polydipsia and a 6.8-kg (15-lb) weight loss. There was no history of recent travel outside of Oregon though the patient had traveled widely in the 1950s while in the service. He had also worked for three years in a tuberculosis sanatorium in the 1940s. Findings on physical examination were unremarkable. A chest roentgenogram showed infiltrates of both apices and posterior upper lobes (Figure 1). Gram's stain of an expectorated sputum specimen showed numerous polymorphonuclear leukocytes, rare epithelial cells and predominant Gram-positive diplococci. Stains for acid-fast bacilli were negative on three occasions. Analysis of urine again showed 20 leukocytes per high power field and bacterial cultures were negative. A tuberculin skin test (5 tuberculin units) was positive with 18 mm of induration. Screening tests of blood chemistries and complete blood count were normal. A pyelogram with dye given intravenously showed mild bladder outlet obstruction and prostatic hypertrophy but no evidence of upper urinary tract disease. The patient was diagnosed as having pneumococcal pneumonia and possible active pulmonary and renal tuberculosis. Treatment with procaine penicillin, isoniazid and rifampin was begun. The patient reported symptomatic improvement and was discharged on a regimen of antituberculous therapy after completing a ten-day course of penicillin.

Second Admission, September 14, 1981

Readmission three days later was prompted by lethargy and orthostatic dizziness. Despite clinical evidence of volume depletion, he was noted to be polyuric. Results of water deprivation tests were suggestive of partial central diabetes insipidus (Table 1).[2] Further evaluation of the patient's hypothalamic-pituitary axis showed the following values: follicle-stimulating hormone, 7.6 mIU per ml (normal, 5 to 20); luteinizing hormone, 3.0 mIU per ml (normal, 5 to 20); testosterone, 76 ng per dl (normal, 300 to 1,100); adjusted thyroxine, 2.4 ng per dl (normal, 4 to 10.5); thyroid-stimulating hormone, 2.3 IU per ml (normal, less than 5.8), and prolactin, 35 ng per ml (normal, 2 to 18). Plasma cortisol levels before and 30 minutes after intravenous administration of 0.25 mg cosyntropin (Cortrosyn) were 5.3 μg per dl and 12.9 μg per dl, respectively. The results were considered typical of hypothalamic dysfunction and replacement therapy with hydrocortisone, levothyroxine and vasopressin was begun. A computerized tomographic (CT) scan of the head showed enhancing lesions in the suprasellar region, left cerebellum and right caudate nucleus (Figure 2). A low-density lesion in the left temporal area was felt most suggestive of an arachnoid cyst. Lumbar puncture done September 30, 1981, showed an opening pressure of 260 mm of water. Cerebrospinal fluid studies are recorded in Table 2. Results of Gram's stain; fluorochrome, india ink, cryptococcal antigen and VDRL tests; cytology examination, and bacterial and fungal

Refer to: Morse HG, Nichol WP, Cook DM, et al: Central nervous system and genitourinary blastomycosis: Confusion with tuberculosis. West J Med 1983 Jul; 139:99-103.

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ABBREVIATIONS USED IN TEXT

CF=complement-fixation
CT=computerized tomography

cultures were negative. Four-vessel cerebral angiography showed left ophthalmic artery and anterior communicating artery aneurysms and the left temporal lesion that again was felt to be an arachnoid cyst. Though tuberculous meningitis was the likely diagnosis, cultures of urine, sputum and cerebrospinal fluid specimens were all negative for mycobacteria at six weeks. Diagnostic bronchoscopy with transbronchial biopsy, brushing and washing specimens was done with cytologic examination, cultures, fluorochrome, Gram's stain and potassium hydroxide preparation. These did not result in a diagnosis. Biopsy specimens of the upper lobes of the lung showed chronic inflammation without organisms or granulomata.

The patient improved symptomatically with rehydration and was discharged receiving isoniazid, rifampin, hydrocortisone, desmopressin acetate and levothyroxine. Two weeks after discharge he was seen in the outpatient clinic and remained improved.

Third Admission, October 24, 1981

The patient was admitted because of confusion, lethargy and pronounced orthostatic hypotension. Neurologic examination showed meningism, ataxic gait and a mild left hemiparesis. Findings on a chest roentgenogram and CT scan of the head were unchanged. Lumbar puncture was repeated October 26, 1981 (Table 2). A large volume cisternal tap showed similar values and smears, cultures and cytologic studies were also negative. Serologic tests of serum showed the following titers: coccidioidomycosis complement-fixing (CF) of 1:8, blastomycosis CF 1:8, histoplasmosis CF 1:32 and cryptococcal antigen test negative. Cerebrospinal fluid electrophoresis showed a polyclonal increase in immunoglobulin G. Culture of expressed prostatic secretions grew an organism initially identified as a *Chrysosporium* and felt to be a contaminant. The culture was sent to the Centers for Disease Control for further identification. A bone marrow biopsy specimen showed no organisms or granulomata.

TABLE 1.—*Water Deprivation Test, Second Admission (September 14, 1981)*

Urine volume for 24 hrs	4,450-5,750 ml
Dehydration period	7 hrs
Maximum urinary osmolality on dehydration	252 mosm/kg water
Urinary osmolality after vasopressin therapy	286 mosm/kg water
Change in urinary osmolality	+34 mosm/kg water (+13.5%)
Plasma osmolality before vasopressin	283 mosm/kg water
Weight change on dehydration	1.4 kg

Recurrent episodes of somnolence were attributed to rising serum sodium content and volume depletion. Vasopressin tannate was given subcutaneously and fluids intravenously to maintain intravascular volume. Ten days after admission, the patient became severely obtunded and an acute right hemiparesis and central hyperventilation developed. A CT scan of the head

Figure 1.—Posteroanterior **(left)** and lateral **(right)** chest films done on first admission (September 1, 1981) showing infiltrates in both apices and posterior upper lobes.

showed no change. Progressive obtundation and respiratory depression necessitated mechanical ventilation. Lumbar puncture was repeated November 6, 1981 (Table 2). Serologic studies of a cerebrospinal fluid specimen for fungus showed histoplasmosis CF titer 1:8, blastomycosis CF titer 1:2 and cryptococcal antigen test negative.

Because of a failure to respond to antituberculous therapy, an uncertain diagnosis and a severely worsening clinical condition, amphotericin B therapy was begun on November 6, 1981, for the possibility that fungal meningitis might be present. Diagnostic craniotomy was done after three days of amphotericin B administration, with biopsy specimens of brain and meninges showing nonspecific inflammation. No microorganisms or malignant cells were identified but the presence of a benign arachnoid cyst was confirmed. A follow-up CT scan showed decreased enhancement of the suprasellar lesion. Over the next several weeks the patient's mental state improved gradually but never returned to baseline. Five weeks after beginning amphotericin B therapy, a repeat lumbar puncture showed a return to normal of cerebrospinal fluid values (Table 2). Subsequently, bacteremia and bilateral lower lobe

TABLE 2.—*Cerebrospinal Fluid Measurements*

Date	*Glucose mg/dl*	*Protein mg/dl*	*Leukocytes*	*Neutrophils Percent*
9/30/81	37	111	610	44
10/26/81	14 (86)*	310	450	49
11/ 6/81†	20 (92)	253	1,285	83
12/12/81	82 (128)	51	15	0

*Simultaneous serum glucose values in parentheses.
†Amphotericin B therapy was begun on November 6, 1981.

aspiration pneumonia developed due to *Staphylococcus aureus*. Following profound and prolonged hypotension, the patient became decerebrate and a CT scan showed decreased density in the entire left hemisphere and a large midline shift, indicating a left cerebrovascular accident. A nuclear brain scan showed no perfusion of either hemisphere. An electroencephalogram showed no cerebral electrical activity and mechanical ventilation was discontinued.

Postmortem Findings

Serologic studies for fungi done on a cerebrospinal fluid specimen obtained just before death showed no change in histoplasmosis, blastomycosis, cryptococcal

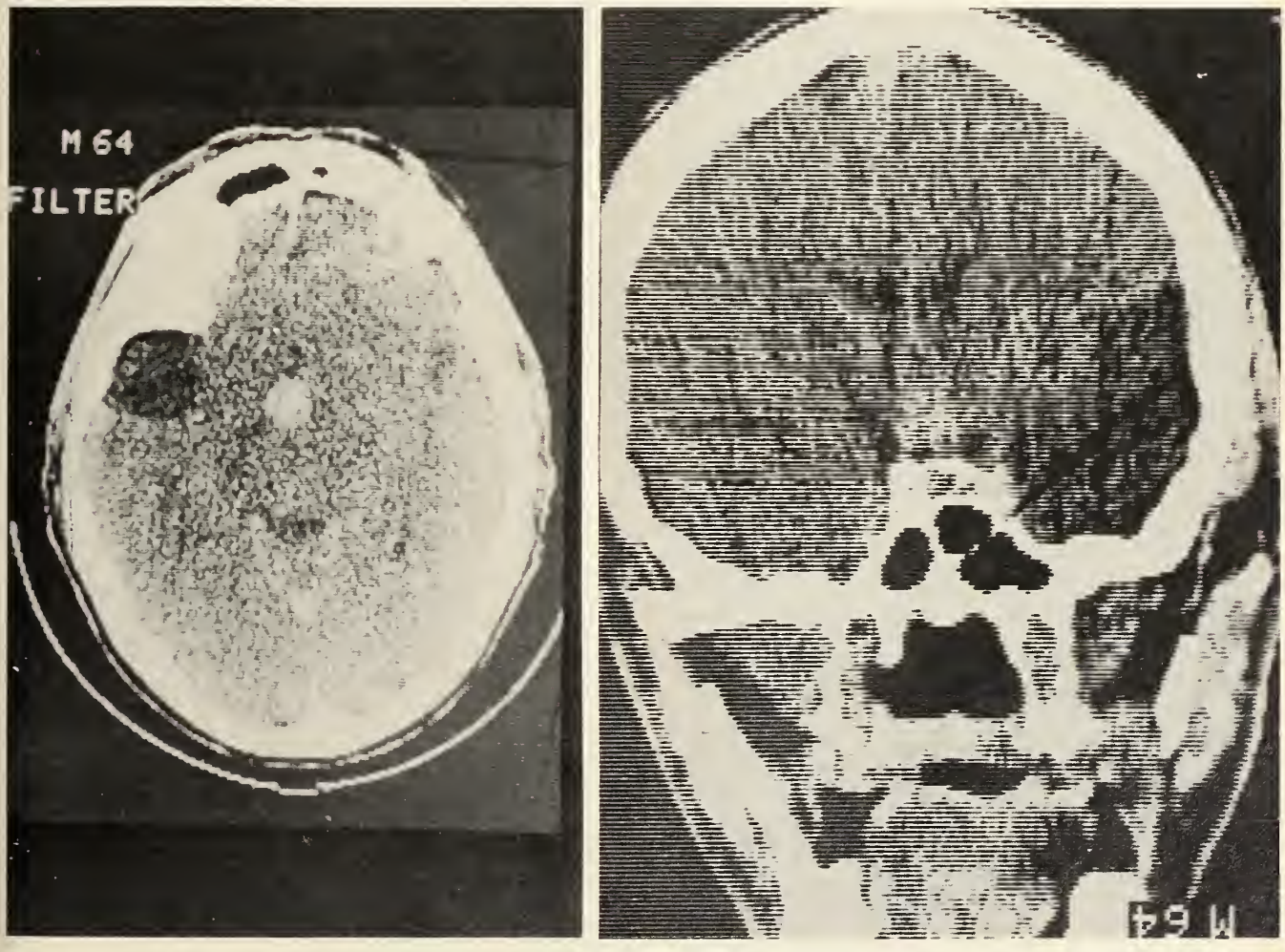

Figure 2.—Computerized tomographic scan of head, axial **(left)** and coronal **(right)** sections, on second admission (September 14, 1981) showing lesions in the suprasellar region, left cerebellum and right caudate nucleus.

or coccidioidomycosis antibody titers. Four weeks after the patient died, culture of the expressed prostatic secretions taken nine weeks before his death was reported by the Centers for Disease Control to be growing *Blastomyces dermatitidis*. Postmortem examination showed extensive central nervous system and prostatic involvement with budding yeast forms on periodic acid-Schiff staining, morphologically typical of *B dermatitidis* (see photomicrographs, Figures 3 and 4). Organisms were identified in both lobes of the pituitary gland, in the pituitary stalk and in the leptomeninges at the base of the hypothalamus. A diffuse perivascular mononuclear cell infiltration associated with budding yeast was found in vessels from the circle of Willis. A recent left hemispheric infarction was present. The remainder of the brain including the hypothalamic region was not sufficiently preserved for accurate pathologic diagnosis. The lungs showed apical scarring and fibrosis without active disease and pneumonia of both lower lobes was found. Acid-fast and periodic acid-Schiff stains showed no organisms in pulmonary tissue. Fungal culture of specimens taken at autopsy from lung, brain and prostate were negative.

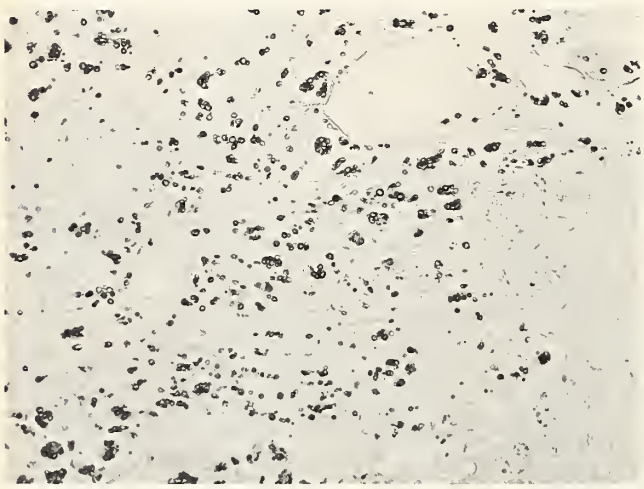

Figure 3.—Secretion of prostate shows numerous budding yeast forms. (Methenamine silver stain, reduced from magnification ×100.)

Figure 4.—Section of nutrient branches of basilar artery, with upper vessel showing vasculitis. (Hematoxylin and eosin stain, reduced from magnification ×100.)

Comments

Although originally felt to be a disease limited to North America, blastomycosis is now recognized to have a worldwide distribution. Endemic areas in North America, as defined by case reporting, include the southeastern and south central United States, as well as the Great Lakes region of the United States and Canada. The disease appears to be distinctly less prevalent west of the Rocky Mountains, though cases have been reported sporadically.[3,4] The precise epidemiology of blastomycosis has yet to be defined. Occupational or recreational exposure to soil enriched with avian excreta has been suggested as a potential source of infection; attempts to culture the organism from soil, however, have usually failed.[4] Our patient's occupation (heavy equipment operator) is likely to have provided ample opportunity for such exposure. No related cases in humans or dogs that would suggest a common source of exposure could be identified.

Pulmonary infection due to *B dermatitidis* can present as acute pneumonia but more often results in minimally symptomatic or asymptomatic pneumonitis. Spontaneous healing and late endogenous reactivation have been observed.[4] The findings on chest roentgenograms in cases of pulmonary blastomycosis are not distinctive, with changes varying from a consolidated lobar pneumonia to multiple diffuse infiltrations. Hilar adenopathy is common but cavitation is rare.[5,6] Our patient's chest roentgenogram showed changes typical of granulomatous disease but without prior films for comparison the activity of disease could not be assessed. Because of a positive tuberculin skin test, the abnormalities were initially considered due to tuberculosis. No evidence of active pulmonary blastomycosis or tuberculosis was found on repeated cultures or histopathologic examination of the lungs either before or after death. Whether the roentgenographic abnormality represented healed blastomycosis or tuberculosis or both cannot be determined.

Central nervous system involvement with blastomycosis is estimated to occur in 3% to 10% of cases. Estimates are as high as 33% in autopsy series.[7] Central nervous system disease presents clinically as chronic meningitis or as intracranial or spinal mass lesions. A similarity between blastomycotic and tuberculous meningitis has been stressed in recent reviews[7,8] and, indeed, the two diseases are indistinguishable on clinical grounds. Serodiagnosis of blastomycosis is insensitive and cross-reaction with *Histoplasma capsulatum* can occur.[4,9] Although a complement-fixation titer of 1:32 or higher should encourage aggressive attempts to diagnose blastomycosis, no single titer is diagnostic of active disease. Skin tests are of no value in diagnosis and are no longer commercially available. More than 90% of reported cases of central nervous system blastomycosis have had culture-negative lumbar cere-

brospinal fluid. Cisternal or ventricular fluid sampling has been considered more sensitive than lumbar puncture,[7,8] but in the current case a large-volume cisternal tap was negative for fungi by both smear and culture despite extensive central nervous system involvement proved at autopsy. Likewise, meningeal and brain biopsy studies showed no abnormalities, although specimens were not obtained from the basal meninges, the area found at autopsy to have the richest fungal invasion. Gonyea[7] has stressed the importance of a vigorous diagnostic search for extraneural disease and that testing should include cutaneous and subcutaneous lesions, joint effusions, large volume urine culture, smear and culture of prostatic secretions or prostatic biopsy. A needle biopsy of the prostate would likely have provided an earlier diagnosis in our patient. Vasculitic response to deep mycotic infection has been well described in cases of histoplasmosis and coccidioidomycosis,[1] but to our knowledge has not been described in those of blastomycosis. Vasculitis may have contributed to our patient's recurrent focal neurologic events.

The male genitourinary tract is involved in 20% to 30% of cases of blastomycosis. Presentation with prostatitis or urinary retention is well documented.[10,11] The importance of aggressive evaluation of a slowly resolving case of prostatitis, including fungal culture of prostatic secretions and a biopsy study, cannot be overemphasized. Culture of expressed prostatic secretions eventually led to a correct diagnosis in our patient but delay in doing this caused a delay in instituting appropriate therapy. Because *B dermatitidis* may require two to three weeks for isolation and identification, histopathologic examination of biopsy material potentially provides a more rapid diagnosis.

Endocrine syndromes caused by blastomycosis have included primary adrenal insufficiency due to adrenal involvement,[12] hyperprolactinemia due to chronic pleural disease[13] and, recently, diabetes insipidus of unclear cause.[14] Pathologic series have described thyroid and pituitary involvement but no clinical data are provided.[1] To our knowledge this is the first reported case of hypopituitarism due to blastomycosis with pathologic correlation. Pathogenesis of this syndrome is evident from the necropsy findings; fungal organisms were found in both lobes of the pituitary and in the stalk. In addition, the area of richest meningeal involvement was that of the median eminence. Hypothalamic invasion was suspected clinically on the basis of an enhancing suprasellar mass on CT scan that diminished in size during amphotericin B therapy. Endocrine evaluation also suggested hypothalamic dysfunction (elevated prolactin level with depressed luteinizing hormone, testosterone, thyroid-stimulating hormone and thyroxine levels). Hypothalamic tissue was not sufficiently preserved at autopsy to show destruction by fungi. The patient's endocrine dysfunction likely resulted from patchy involvement of both the pituitary and the hypothalamus with blastomycosis.

Finally, the differential diagnosis between tuberculosis and blastomycosis deserves comment. These infections can be clinically indistinguishable and, in fact, have been reported to occur simultaneously.[15,16] Our patient's presenting symptoms of fever, night sweats and weight loss, coupled with a positive tuberculin skin test and findings on a chest roentgenogram typical of tuberculosis, led to the empiric administration of antituberculous therapy while awaiting culture confirmation. Chronic meningitis, sterile pyuria and hypothalamic dysfunction are all well described in cases of tuberculosis; however, several aspects of this case suggested a cause other than mycobacteria. Abnormal upper urinary tracts on a pyelogram with dye given intravenously are seen in more than 90% of patients with genitourinary tuberculosis[17]; therefore, the normal findings on our patient's pyelogram should have prompted search for an alternate cause of sterile pyuria. Of the deep mycoses only blastomycosis commonly involves the lower genitourinary tract.[11] Prostatic biopsy would likely have provided an earlier diagnosis and avoided more invasive diagnostic procedures. Second, his failure to respond to empiric antituberculous therapy and the development of progressive chronic meningitis while receiving therapy would be unusual for tuberculosis. Failure to show improvement by cerebrospinal fluid measurements after eight weeks of isoniazid and rifampin therapy should prompt search for other causes of chronic meningitis.[18,19] Ventricular fluid sampling and brain and meningeal biopsy studies, although unrewarding in this case, may be indicated in the search for a specific diagnosis. Blastomycosis should be considered in the differential diagnosis of any systemic illness resembling tuberculosis, even when it occurs outside the usual endemic areas.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

More on the Medical Consequences of Nuclear War

TO THE EDITOR: The ostensible purpose of the four articles on the predicted medical consequences of nuclear war in the February 1983 issue was to convince readers that "prevention of nuclear war is the only alternative worthy of our pursuit."[1] But do physicians need to be convinced? Does anyone seriously believe that there is a significant number who *don't* advocate prevention of nuclear war? Why, then, publish a "symposium"?

Curiously, the authors say very little about the *means* by which nuclear war is to be prevented. Dr Cassel states that "there is no political reason on earth that can morally justify the continued uncontrolled existence of [nuclear] weapons,"[2] but she offers no plan for controlling those weapons, especially those in the possession of the Soviet government. Dr Lipton is equally vague, but seems to think that going to a lot of meetings will somehow help.[3] Dr Hollingsworth mentions the "gentle forbearance" of the Japanese A-bomb victims as "a goad to what we can do," then mysteriously refrains from stating what we can do.[4]

Why the great reluctance and hesitation to recommend a solution? Is what they have in mind too embarrassing? Dr Kornfeld gives us a clue: "The opportunity exists . . . to *freeze* the further development of nuclear weapons"[5] [emphasis mine]. Does this mean that Dr Kornfeld and the other authors are advocating the so-called "nuclear freeze"? I sincerely hope not.

As prophylaxis for nuclear war, the "freeze"—a code word for a trust-the-Russians scheme which would seriously restrict our self-defense options—would be as effective as a garlic necklace.

Concerning the prevention of nuclear war, the essential question for Americans is this: Do we need nuclear weapons for "deterrence" or don't we? If we don't, we should ban them all *unilaterally;* their mere existence is unacceptably dangerous. If we do need them, then we need an *effective* deterrent, not a placebo, and certainly not the kind of "deterrent" limited by treaty with a self-declared enemy.

The "freeze" proposal, though it may be popular, is not a rational compromise between the two alternatives. It is the worst of both worlds. It would guarantee enough computer-triggered nuclear missiles to maintain the peril of accidental nuclear holocaust, but *not* enough to convince the Politburo that a nuclear war is unwinnable (for them).

Physicians, like all Americans, must eventually choose between the only real alternatives: unilateral disarmament or a genuinely *defensive* weapons system, not crippled by any treaties, which could assure destruction of incoming nuclear missiles before they do damage to the biosphere.

Somehow I got the feeling that the "symposium" was a sort of soft-sell pitch for the "nuclear freeze," and that disturbs me. The risk of nuclear war may be a significant medical issue, but *The Western Journal of Medicine* is no place to peddle snake oil.

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* * *

TO THE EDITOR: With the publication of its fine series on the medical consequences of nuclear war,[1] the *Western Journal* has begun to meet its responsibility to educate physicians about this supreme health issue. This is in keeping with resolutions by the American Medical Association (*The New York Times,* December 10, 1981, "AMA Vote on Arms Peril Bids Doctors to Take Action") and numerous local and state medical associations—among them the California Medical Association (CMA House of Delegates Resolution 3a-82: "Medical Consequences of Nuclear Weapons") calling for such educational efforts.

The next step in this process is suggested by the passage of a resolution by the California Medical Association's House of Delegates in March 1983. It calls upon the association to "work with state authorities to develop contingency plans for dealing with the medical consequences of limited or all-out nuclear war" and to "present a similar resolution to the AMA for a cohesive nationwide plan to deal with the public health consequences of nuclear war" (Resolution 17-83).

This is a departure from previous public statements

by both the AMA and the CMA that "in the event of a nuclear holocaust, no adequate medical response is possible" (*The New York Times,* as cited above). The CMA has thus obligated itself to expand upon the article in the February issue by Dr Howard Kornfeld[2] and explore, for its membership, every aspect of current civil defense preparations for nuclear warfare, including the ramifications of organized medicine's participation in such planning. The public will correctly perceive cooperation in planning for limited nuclear war as approval of the Reagan administration's Crisis Relocation Plan and of the Defense Department's Five-Year Defense Guidance.

The Crisis Relocation Plan is a $4.2 billion plan to remove two thirds of the US population—145,000,000 people—from "high-risk" urban areas to "low-risk" host areas in the several days preceding the outbreak of nuclear warfare. The Federal Emergency Management Agency (FEMA) claims that up to 80% of the US population would survive nuclear war's immediate effects, and that the country could then be rebuilt in "a relatively short time" (*Los Angeles Times,* January 15, 1982, "U.S. Will Revive Civil Defense"). The plan also plays an important military role. Last May it was learned that the Department of Defense has ordered its forces to prepare to wage "protracted nuclear wars" in such a way that the U.S. would "prevail" (*The New York Times,* May 30, 1982, "Pentagon Draws Up First Strategy for Fighting a Long Nuclear War"). A credible civilian defense program is necessary to back up the threat to wage such a war, because of the obvious danger of retaliation against civilian populations. In order to be credible threats, counter-silo missiles, such as the MX, Trident II, Pershing II and Cruise, *require* civil defense.

Before physicians condone a nuclear war-fighting strategy and the Crisis Relocation Plan, they should ask a few basic questions: (1) Are the underlying assumptions sound? These include faith in controllability and limitation; adequate warning; foreknowledge of targeted and spared areas; human behavior under unprecedented stress; crisis stability after activation of evacuation; ecological stability after nuclear cataclysm. (2) What survival is really possible even if all the assumptions are correct? Short-term survival is hardly satisfactory. Neither is mere continuation of the species. What about our culture? Our nation? Can civilization be "hardened"? (3) Is medical participation only a humanitarian act, or will physicians be participating in a plan to make nuclear weapons seem less devastating —more usable and thus more likely to be used?

Physicians naturally want to *do something* in the face of impending disaster. The public does not need us, however, to tell them that they would be better off in a remote area with several years' stocks of food, medicine and ammunition. The "state authorities" with whom the CMA has resolved to work, however, might need the silent approval of organized medicine in order to implement a dangerous and naive plan. Certainly, physicians must not allow themselves to be used by those who agree that the "United States must possess the ability to wage nuclear war rationally" (*Foreign Policy,* Fall 1980, "Victory Is Possible"). We know better. We must resist the attempt to conventionalize nuclear war by lumping it with lesser events for which we ought to prepare. There really *is no adequate* medical response to nuclear holocaust. The sooner our national security is based on this fact the safer we will be.

PETER G. JOSEPH, MD
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President, San Francisco Bay Area Chapter
Physicians for Social Responsibility

(This letter was also signed by Howard M. Slyter, MD; John E. Adams, MD; Melvin M. Grumbach, MD; Phillip R. Lee, MD; Alan Margolis, MD; Kenneth L. Melmon, MD; Robert S. Wallerstein, MD, and Warren Winkelstein, Jr, MD, MPH.)

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* * *

TO THE EDITOR: Congratulations on your wisdom in taking the question of "Medical Consequences of Nuclear War" seriously, as evidenced by the February 1983 issue. I agree that physicians should know more about the potentially horrible effects of widespread nuclear attack, not only for purposes of prevention, but also because it is possible that we may someday be called upon to help—for instance, in case of a nuclear accident or a limited attack by terrorists.

In this sense, the article "Nuclear Weapons and Civil Defense"[1] by Dr Howard Kornfeld is largely in error, and deserves serious reply. I do not dispute the point that he and Physicians for Social Responsibility have made so often: All-out nuclear attack by the USSR on our urban population would completely overwhelm our current medical capabilities. However, there are many other possible scenarios of nuclear disaster, including weapons accident, attack by a government other than the Soviet, "demonstration explosion" to illustrate the seriousness of a threat, as was proposed against the Japanese in World War II, and the like. Kornfeld himself admits to "the growing possibilities for accidental or unauthorized nuclear war."

Furthermore, we are not privy to the war plans and targeting strategies of the USSR. It is entirely possible that an attack could come with the first round directed at nuclear missile sites, air bases, submarines and other military targets, with industrial and population targets held back for a second or third round. If hostilities stopped after such a beginning, hospitals, physicians and other health professionals would largely survive, and be called upon to care for the casualties.

Kornfeld tries to indict us all for contributing to the previous nuclear arms race, claiming that "the medical profession uncritically endorsed a civil defense plan for all-out nuclear war." American physicians never endorsed any plan for all-out nuclear war, and now, as then, have given priority to the saving of life and the

prevention of suffering, no matter what the circumstances.

There are many other problems with Dr Kornfeld's article and with the other related articles in the issue. Serious discussion requires more space than is appropriate for a letter to the editor. I am preparing an original article on medical and ethical arguments for civil defense, and will submit this as soon as possible.

HOWARD D. MACCABEE, PhD, MD
Walnut Creek, California
*President, Doctors for Disaster Preparedness**

*DDP is a new organization of physicians, scientists and health professionals, which endorses the idea that it is an ethical imperative to attempt to save lives and alleviate suffering in any type of catastrophe, whether it be man-made or natural, large or small, nuclear war, accident, terrorism or any other disaster.

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* * *

To the Editor: During the past several years, I have felt *The Western Journal of Medicine* to be an excellent journal with well-researched, well-written articles. The February issue represents a marked change from that tradition and reputation. The articles on nuclear war belonged in the *National Enquirer* rather than *The Western Journal of Medicine*. I agree completely that nuclear war would be the greatest catastrophe that ever has or ever could appear on our planet. The *thought* of nuclear war and its consequences, however, is a reality that we cannot and should not ignore. Rather than stating that the majority of physicians and medical facilities would be destroyed or incapacitated, and therefore no plans should be made, it would be more appropriate to consider how the small remnants of medical resources can be organized to provide optimal care under the worst of circumstances. I have been involved in the care of the victims of a plane crash in Bolivia; supplies were inadequate and the hospital did not even have hot running water. Rather than screaming "we can't do it," adaptations and modifications were made such that the care of these victims, while perhaps not absolutely optimal, was certainly more than adequate. There is no way that my burn center or even hospital could handle all of the victims from a major airport or BART (San Francisco Bay Area Rapid Transit system) disaster. Nonetheless, we do have a plan for how we would handle what we could and triage what we could not.

I have always thought that physicians were morally committed to treat the victims of disease or injury no matter what the cause or the socioeconomic or political status of the victim. We treat prisoners of war as well as victims of war. By what logic do the so-called Physicians for Social Responsibility justify refusal to plan to treat victims of a war that they may oppose or the means by which it is fought? To slightly paraphrase Voltaire, I will defend to my vaporization in a nuclear fireball the right to object to that fireball, but I will condemn until the same time the refusal to consider how to treat those who are not at ground zero.

If *The Western Journal of Medicine* is going to print sociopolitical articles, then I feel it is only appropriate to request invited dissent in the same issue. Failure to do this converts it to "The Western Journal of Politics."

JEROLD Z. KAPLAN, MD
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* * *

To the Editor: I was most interested in the articles included in the February issue dealing with the consequence of nuclear war. Please envision the following scenario:

A long, long time ago, caveman Glumpf was walking among the rocks near his cave using a stick to balance himself. As he walked, a wild boar jumped at him. He lunged to get away and as he fell his stick was split by a rock on the ground. He used his stick, with rock attached, to hit and kill the boar.

That night, while he and his fellow cavemen ate the boar, he showed them his new tool (weapon); it's merits were discussed. All the men grunted the following over and over: *"Mimika, paga paga, oomph"* (translated: "Awesome"). Finally, one of the cavemen asked Glumpf if he would ever use his weapon (tool) on some of those pesky cave people on the next mountain. Glumpf thought about this and replied: *"Ook, ba goo whatka youra thinka."* Translated, this means "I would only show it to them to indicate what power I had, thus deterring a face-to-face conflict. Only under a severe and life-threatening situation would I utilize the mind-boggling power of this weapon."

Three days later, while hunting for food, Glumpf and some comrades accidentally came upon several members of that nearby tribe. Without thinking of any repercussions for all of mankind, he attempted to hit each one on the head with his new weapon (". . . to end all weapons"). Unfortunately for Glumpf, a member of the other tribe had also stumbled upon the idea for such a weapon. As the weapons cut the air, one by one, the members of the two tribes were felled. Finally, Glumpf made a lunge at the final member of the other tribe. Tragically, this final adversary with the weapon also made a final lunge at Glumpf. Would you believe that the blows hit simultaneously and both men were killed? Alas, the end of the story.

Now, please reassure me that someone in a high government position isn't related to Glumpf; because if one of his relatives has the same mentality, perhaps we had all better get accustomed to sitting around fires in caves—that is, those of us who are left after the mutual destruction. Perhaps one of us might even rediscover the wheel.

DANIEL A. GROSS, MD
Tarzana, California

* * *

To the Editor: Intellectual incest is not the usual *WJM* pattern. If your February subject were indeed the "Medical Consequences of Nuclear War," then my 1952 *Flight Surgeon's Manual* reveals nearly as much scientific information. I therefore infer that your greater purpose was to arouse interest in *prevention*. However, your presentation implied common sense to only one

of the two widely held viewpoints on how best to prevent nuclear war: to freeze first, then trust to negotiations. The viewpoint held by most persons with the best knowledge of the Soviets is to first motivate them to reduce armaments by modernizing our own.

The Communist party's aim is to impose a communal way of life on all peoples by violence and deceit—much as Hitler also outlined for the Nazi party in *Mein Kampf*. Hindsight suggests that Neville Chamberlain's trust of Adolph Hitler cost hundreds of millions of lives (some in fire storms similar to those of nuclear war). The equivalent of our second viewpoint above was Churchill's plea to modernize deterrents. The biggest policeman is the one least apt to be challenged to fight. The best way to avoid war is to stay strong—according to George Washington.

In case you need knowledgeable authors to balance the views on prevention of nuclear war, I suggest physicist William Shuler, Lawrence Laboratory, Livermore, California, who writes, "What could stop the Soviets from violating the freeze? I, for one, do not want to live under their system." Also, Assistant Secretary of Defense Richard Perle seems to articulate great knowledge of factors for prevention of nuclear war. When we question the need for surgery, are we wise to hear from the surgeons (preferably in the same issue)? When we have symposia on the horrors of biological warfare or of chemical warfare (very appropriate subjects for future *WJM* issues) would we better avoid inbreeding of ideas by including the biologists, the chemists and, above all, those we have made responsible for prevention?

HOWARD F. LONG, MD, MPH
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* * *

TO THE EDITOR: *The Western Journal of Medicine* is to be commended for publishing the symposium on the Medical Consequences of Nuclear War in February. Although we have lived with an awareness of this increasing problem since 1945, it has appeared to have little effect on most of our lives. There have been, however, important psychological phenomena. Undoubtedly, some denial of the seriousness of the issue is a partial explanation of our silence until the world now has 60,000 nuclear weapons. A subconscious influence on our society has probably been a factor in problems of crime and personal strife of many types.

Carefully studying the almost incomprehensible medical, social and environmental problems, the reader may feel overwhelmed and quite depressed. After a period of reflection and consideration of this subject, many have found an energizing realization that the horrible scenario has not taken place and that this can and must be avoided. The prevention of a nuclear disaster may well be the most important medical issue in history.

Peace movements have come and gone over the years, but there is presently a growing momentum, including nuclear arms control, that is not about to stop. The reason is simply that there has never been a situation like we have today, and there is now no acceptable alternative to truly investigating international conflict resolution. This is not a naive concept. If clear thinking can prevail, and it probably will, we can be optimistic not only that nuclear war can be avoided, but that a new level of human understanding can come about. Such beautiful dreams are not new and attempts at world government with policing activities have been only partially successful, but again there has never been an adequate reason to make it work. As Dr Judith Lipton said, "Yet, by beaking through the denial and fatalism and becoming involved in an active way on behalf of our children and the planet, we have an opportunity to find enhanced meaning."[1] The "Medical Consequences of Nuclear War" is heavy reading, but there is possibly the greatest opportunity that mankind has been offered—just over the horizon.

In primitive times, people honestly had fear of the unknown on the other side of the mountain. Extensive resources, experience and communication have eliminated to a large degree that enormous stumbling block. There is no choice at this time but to honestly negotiate for peace in the world and for control and the gradual elimination of nuclear weapons. We should not feel helpless and, therefore, become ineffective because of the magnitude of the problem. Physicians continue to work for life and health and for the prevention of epidemics and disease.

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REFERENCE

1. Lipton JE: The last traffic jam (Medical Consequences of Nuclear War Symposium). West J Med 1983 Feb; 138:222-226

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EDITOR'S NOTE

The above letters are representative of many more that have been received from obviously concerned readers who have taken the time to respond to the symposium on the Medical Consequences of Nuclear War which appeared in the February issue. The editors believe these fairly reflect most of the comments received. Because of space limitations it is likely that no further correspondence will be published concerning this symposium.

—MSMW

No Elbow Damage in Young Baseball Pitchers

TO THE EDITOR: As a physician and youth-league baseball coach, I have been asked whether pitching imposes significant risk of enduring damage to the elbows of young players. Only recently has this issue been subjected to scientific investigation.

Gugenheim and co-workers[1] examined 595 Little League pitchers ages 9 to 13 in Houston. It was noted that elbow x-ray findings fall into two categories: (1) quite common anatomic variants that do not correlate with any symptoms or problems and (2) quite uncommon, potentially disabling abnormalities (osteochondrosis/avascular necrosis/osteochondritis dissecans) that are apparently unrelated to athletics. No correlation

was found between years of pitching experience and any elbow symptoms or problems.

Larson and associates[2] examined 120 pitchers ages 11 and 12 in Eugene, Oregon. There were no statistically significant correlations or interrelations found regarding pitching experience, symptoms, elbow deformities or x-ray findings. The authors concluded that "pitching demands in Eugene have not been demonstrated to be detrimental to the immature throwing arms."

Responding to concern about the possibility that adverse effects might be delayed in their appearance, Francis and associates[3] studied 328 Brigham Young University students who had played youth-league baseball, and compared them with 70 students with no previous baseball experience. No significant difference was seen in incidence of residual damage, or in residual injury among positions played or years of experience. The conclusion was that "participation in organized baseball as an adolescent has no enduring deleterious effect on the throwing elbow."

Likewise, Grana and Rashkin[4] studied 73 Oklahoma City senior high school pitchers. No significant relationships were found between occurrence of symptoms and number of seasons played, individual pitching traits, asymmetry on physical examination or asymmetry on x-ray examination of the elbow.

In other words, recent studies tend to contradict the widely held belief that pitching a baseball imposes significant risk of enduring damage to a young player's elbow.

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CSN Codes for Specialized Occupational Medicine Services

TO THE EDITOR: The excellent collection of articles on occupational medicine topics in the December 1982 issue will be a stimulus to the provision of occupational medicine services by providers in the West. We recently proposed a set of model service codes for specialized occupational medicine services compatible with the format of the 1974 revision of the California Relative Value Studies (RVS)[1] and are using it for routine billing and administrative procedures. We propose it as a standard for other medical groups and for possible inclusion into the planned update of the California Standard Nomenclature (CSN) directed by the 1981 House of Delegates of the California Medical Association.

The majority of clinical services provided by occupational medicine practitioners are comparable to those already encoded in the CSN, differing only in the cognitive skills of the practitioner. A few common services are unique to occupational medicine, however, because they pertain to on-site plant visits, extensive consultations with employers, and urgent consultations to deal with a hazardous situation or other problem. These services have no identifiers in the present CSN, but occur sufficiently often to require a code number for billing and data management purposes.

The 1974 RVS has a gap in the numerical sequence in the 98000 series; these numbers are also unused in the AMA Current Procedural Terminology. Why this gap exists is not known, but its placement just before the "Special Services" section is very fortunate. We developed a coding system within the 98000 sequence (Table 1) which is based on the following scheme: The third digit represents *activity* (0=exploratory discus-

TABLE 1.—*Proposed Numerical Codes for Specialized Occupational Medicine Services, Compatible With CSN*

Suggested Code	*Name of Service*	*Description of Service*
98001	Initial On-Site Consultation	Visit to client's location to ascertain client's needs, requiring approximately 1 hour.
98011	Initial Office Consultation	Visit by client to provider's office to ascertain client's needs, requiring approximately 1 hour.
98101	Consultation Visit, On-Site	Visit to client's location to evaluate a particular problem.
98131	Routine Telephone Consultation	Telephonic consultation concerning an uncomplicated problem, approximately 30 minutes duration.
98201	Health Hazard Evaluation	Extensive survey and evaluation of problem, may require team of professionals.*
98301	Follow-Up, Limited	Visit to plant to evaluate progress, approximately 3 hours.
98302	Follow-Up Evaluation	Visit to plant to assess progress in a complex situation.
98401	Emergency Visit, On-Site	Visit on short notice to client's location to assist with problem which is urgent.
98431	Emergency Telephone Consultation	Telephonic consultation on an urgent problem not requiring presence on-site, approximately 30 minutes.
98501	Instructional Visit, On-Site	Visit to client's location to arrange or present a scheduled instructional program.
98921	Consultation Service	Time spent in research, report preparation, or conceptualizing approach and solution to problem.

*Members of such a team may include industrial hygienists, safety engineers, epidemiologists, toxicologists, and specialized technical personnel as appropriate.

sion, 1 = consultation, 2 = health hazard evaluation, 3 = follow-up, 4 = emergency, 5 = scheduled activity such as an educational presentation, 9 = research and literature review). The fourth digit represents *location* (0 = client's site, 1 = medical facility, 2 = information resource such as a library or data bank, 3 = telephonic communication). The fifth digit is a specific identifier. This scheme has been flexible enough to cover all situations we have encountered but has ample latitude for expansion. The codes are now programmed into our computer and can be independently adjusted for changes in fee schedule.

We urge that the obsolete code 99060 "environmental intervention" be abandoned as inadequate for describing occupational medicine services and that a system similar to ours be considered for inclusion into CSN. Incidentally, codes already exist for multiphasic health testing (99090) and administration of a programmed medical interview (99095).

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Kaposi's Sarcoma of the Rectum

To the Editor: Unlike the classic form of Kaposi's sarcoma, which occurs most frequently in elderly men and is characterized by nodules on the lower extremities, the cases now being seen in connection with the acquired immune deficiency syndrome (AIDS) are occurring in much younger (often homosexual) men and lesions may be found on any part of the body. As Dr Robert L. Modlin points out in the June 1983 issue, "Skin lesions can present as single or multiple reddish purple macules, nodules or plaques on any location of the skin or mucous membranes."[1] Fever, weight loss, diarrhea and lymphadenopathy in many cases precede appearance of lesions. The purpose of this brief report is to make clinicians aware of the variable presentation of the disease, as well as noting a specific case.

Report of a Case

A 43-year-old gay, white businessman was seen in May 1983 in surgical consultation for rectal bleeding of three to four months' duration. The bleeding was apparent only at the time of bowel movements and consisted of 5 to 20 ml (patient's estimate) of dark red blood with small amounts of bright red blood. There was no discomfort. About six months earlier the patient had noted the onset of night sweats, daily temperature spikes as high as 39°C (102°F), recurrent episodes of bronchitis, episodic diarrhea due to enteric pathogens (which was treated) and extreme fatigue. There was no weight loss. He had recovered from hepatitis four years before.

On physical examination no lymphadenopathy was noted other than a few shotty inguinal nodes. The liver edge was palpable but smooth and nontender. The spleen was not palpable. There was a fine miliary light pink skin rash predominately on the extremities. This was asymptomatic.

Digital rectal examination revealed two lesions on the anterior wall just proximal to the mucocutaneous line. These were very firm to palpation—somewhat more so than a scirrhous carcinoma. On endoscopy the larger lesion was 0.5 by 0.5 by 5 cm and "pillar-like" in gross appearance. There was a smaller satellite lesion. These were on the mucosa, freely movable and bled easily when touched with a cotton-tipped applicator. They were a deep purple in color. Chest x-ray films, a barium enema study and sigmoidoscopy showed no additional abnormalities. Aspartate aminotransferase (formerly designated SGOT), alanine aminotransferase (SGPT), lactic dehydrogenase and alkaline phosphatase were elevated but minimally so. A VDRL test was nonreactive. The lesions were excised along with a cuff of normal appearing mucosa. Examination by the Department of Pathology, St Francis Hospital, San Francisco, showed them to be Kaposi's sarcoma. The patient was thereafter referred to appropriate facilities at the University of California, San Francisco.

JOHN L. BRADIN, Jr, MD
San Francisco

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Topics in Primary Care Medicine

The Diagnosis of Acute Pelvic Pain

MARTIN QUAN, MD; RICHARD JOHNSON, MD, *and* W. MacMILLAN RODNEY, MD, *Los Angeles*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Acute pelvic pain in women of reproductive age is a major diagnostic challenge to primary care physicians. Numerous studies have shown that a diagnosis based solely on the history, physical examination and simple laboratory data is frequently inaccurate. Much of the morbidity and mortality associated with its different causes can be attributed to delays in establishing the correct diagnosis.

The magnitude of the problem is well illustrated by the medical and socioeconomic consequences of two of the most important causes of acute pelvic pain, ectopic pregnancy and acute pelvic inflammatory disease. Ectopic pregnancy accounts for 10% to 15% of maternal deaths in the United States and it is the leading cause of death in the first trimester of pregnancy. Acute pelvic inflammatory disease afflicts nearly 1 million American women each year and is responsible for 212,000 hospital admissions and 2.5 million outpatient visits annually; direct and indirect costs of the disease approached $3 billion in 1979. Moreover, both pelvic inflammatory disease and ectopic pregnancy play significant roles in the 10% involuntary infertility rate among American couples.

During the past decade, advances in pregnancy testing, ultrasound technique and laparoscopy have greatly strengthened clinicians' diagnostic armamentarium. We will focus on the clinical features of acute pelvic pain with special emphasis on the diagnostic tools available.

Difficulty in Establishing a Diagnosis

The differential diagnosis of acute pelvic pain is described in Table 1. Principal considerations include acute pelvic inflammatory disease, ectopic pregnancy, acute appendicitis, endometriosis and complications of an ovarian cyst. Difficulty is frequently encountered by clinicians in differentiating the possible causes and establishing the correct diagnosis. Jacobson and Westrom examined by laparoscopy 814 women felt clinically to have acute pelvic inflammatory disease and were able to confirm the diagnosis in only 65% of cases. About 23% of the patients had no pelvic abnormalities and 12% had other pathologic conditions, including acute appendicitis, ectopic pregnancy, endometriosis and corpus luteal bleeding.

In another laparoscopic study, Anteby and associates found that the clinical diagnoses of ectopic pregnancy and acute appendicitis were also unreliable, with the prelaparoscopic diagnosis being confirmed in less than 25% of cases. Acute pelvic inflammatory disease frequently mimicked both of these conditions, accounting for more than half of the cases misdiagnosed as acute appendicitis. In view of these and similar data, it has been estimated that for every 100 cases of the disease diagnosed clinically, four patients with ectopic pregnancy and three patients with acute appendicitis are mistakenly treated for it.

History and Examination

Important information to elicit from a patient who has acute pelvic pain is given in Table 2. Characteristics placing a woman at increased risk for pelvic inflammatory disease include the presence of an intrauterine contraceptive device, age between 15 and 25 years, single with more than one sex partner, a male partner who has symptoms of urethritis, a history of gonococcal cervicitis and a history of pelvic inflammatory disease. Similarly, a history of delayed menses, abnormal uterine bleeding or a prior incidence of ectopic pregnancy

Refer to: Quan M, Johnson R, Rodney WM: The diagnosis of acute pelvic pain (Topics in Primary Care Medicine). West J Med 1983 Jul; 139: 110-113.

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should immediately suggest a possible ectopic gestation. The absence of sexual activity during the months preceding the onset of pain should exclude a pregnancy-related cause for a patient's pain. Women reliably using oral contraceptives should not ovulate and thus are at decreased risk for both ectopic pregnancy or the complications of a functional ovarian cyst. Although the intrauterine device does not predispose a woman towards having an ectopic pregnancy, the risk of a pregnancy being ectopic is increased 6-fold to 12-fold if it occurs with a device in place.

Following the history taking, a careful physical examination should be done, with particular emphasis being on abdominal and pelvic findings. Physical findings of importance include a raised temperature; orthostatic changes in blood pressure and pulse; abdominal or pelvic (or both) peritoneal signs; a mucopurulent cervical discharge; cervical motion tenderness; abnormalities in uterine size, shape and consistency; the presence and consistency of any adnexal mass or fullness; adnexal tenderness, and nodularity of the uterosacral ligaments.

Although the history and physical examination may suggest the cause of a patient's complaint, clinical findings generally lack sensitivity and specificity for consistently making an accurate diagnosis. This is clearly evidenced by Table 3, which compares selected signs and symptoms found in ectopic pregnancy, acute pelvic inflammatory disease and adnexal torsion. In view of the unreliability of clinical findings, adjunctive diagnostic studies assume an important role in the evaluation of acute pelvic pain.

TABLE 1.—*Differential Diagnosis of Acute Pelvic Pain*

Pregnancy-Related
- Ectopic pregnancy
- Abortion
  - Septic
  - Incomplete
  - Threatened
- Intrauterine gestation with corpus luteal hematoma

Gynecologic
- Acute pelvic inflammatory disease
- Ovarian cyst (torsion, hemorrhage or rupture)
- Endometriosis
- Uterine leiomyoma
- Pelvic neoplasia

Nongynecologic
- Acute appendicitis
- Urinary tract infection

TABLE 2.—*Information Useful in Evaluating Acute Pelvic Pain*

- Age
- Gravidity, parity
- Menstrual history
- Characteristics of pain
  - Onset
  - Duration
  - Severity
- Associated symptoms
  - Urinary symptoms
  - Nausea, vomiting
  - Vaginal discharge
  - Fever
  - Abnormal uterine bleeding
- History of pelvic inflammatory disease or ectopic pregnancy
- Method of contraception
- Symptoms of urethritis in male partner
- Sexual history
  - Marital status
  - Number of sex partners
  - Current sexual activity

TABLE 3.—*Selected Signs and Symptoms of Ectopic Pregnancy, Pelvic Inflammatory Disease (PID) and Adnexal Torsion*

Symptom or Sign	*Ectopic Pregnancy Percent*	*Pelvic Inflammatory Disease Percent*	*Adnexal Torsion Percent*
Abdominal pain	96-99	94-99	83-100
Amenorrhea	68-93	..	7-23
Vaginal bleeding	55-74	36	7-9
History of PID	16-26	21	..
Cervical motion tenderness	43	97	14
Adnexal tenderness	72-96	92-100	57-78
Bilateral adnexal tenderness	33	93	26
Adnexal mass	53-66	25-49	69-97
Fever	2-7	33	10-25

Simple Laboratory Studies

Complete Blood Count

Although frequently done during the evaluation of acute pelvic pain, a complete blood count is neither sensitive nor specific. Only 28% of patients with ectopic pregnancy are found to have hematocrits of less than 30% and 38% have values above 38%. Furthermore, 50% of patients with pelvic inflammatory disease have a normal leukocyte count and up to 15% of patients with ectopic pregnancy are found to have a leukocyte count above 15,000 per μl.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate is a nonspecific indicator of inflammation. Although classically elevated in acute pelvic inflammatory disease, it has been normal (less than 15 mm per hour) in up to 25% of cases of the disease documented laparoscopically.

Routine Urine Analysis

Microscopic examination of the urinary sediment to determine the degree of pyuria is an accepted method to screen for a urinary tract infection. However, an inflamed appendix in a retrocecal or pelvic position can also produce a significant pyuria and hematuria.

Cervical Gram's Stain

Although considered a poor screening test for gonorrhea in an asymptomatic woman, Gram's stain of cervical exudate has been—as noted by several investigators—a valuable aid in women suspected clinically of having acute pelvic inflammatory disease. As Eschenbach found, using a criterion of "Gram-negative diplococci seen within three or more neutrophils" for a posi-

tive result for gonorrhea leads to a sensitivity as high as 67% and a specificity of 98% being reported. A positive result is considered presumptive evidence for the diagnosis of gonococcal pelvic inflammatory disease. The accuracy of this test, though, varies with the skill of the microscopist.

Examination of the Sex Partner

If available for examination, the sex partner of the patient should be evaluated for the presence of urethritis, which would provide strong supporting evidence for the diagnosis of pelvic inflammatory disease. Because a substantial number of men who have gonococcal or nongonococcal urethritis are asymptomatic, Gram's stain and culture should be done even if the partner says he does not have symptoms.

Pregnancy Testing

Pregnancy testing is an essential aid to the diagnosis of acute pelvic pain because it can distinguish between gestationally and nongestationally related causes. To use these tests effectively, however, a clinician must know the capabilities and limitations of the pregnancy tests available.

Urine Pregnancy Tests

Traditional urine slide and tube tests are generally unreliable for diagnosing ectopic pregnancy because of their lack of sensitivity. The latex slide tests, with a sensitivity for human chorionic gonadotropin of 2,500 ±1,000 mIU per ml, detect only 50% of ectopic pregnancies. The standard tube tests can detect human chorionic gonadotropin levels ranging from 500 to 1,200 mIU per ml but are still negative in 15% to 35% of cases of ectopic pregnancy. Urine ultrasensitive tube tests have recently been developed that possess an increased sensitivity for human chorionic gonadotropin (200 to 250 mIU per ml). Although promising, their role in the evaluation of acute pelvic pain awaits further investigation.

Serum Pregnancy Tests

Recent advances in serologic testing for pregnancy include the radioreceptor assay for human chorionic gonadotropin and the radioimmunoassay for the β-subunit of human chorionic gonadotropin. The radioreceptor assay is capable of detecting serum human chorionic gonadotropin levels as low as 200 mIU per ml and has been reported as being positive in up to 94% of cases of ectopic pregnancy. The β-subunit radioimmunoassays are even more sensitive than the radioreceptor assays and are available as both a qualitative and a quantitative test. The qualitative radioimmunoassay can detect human chorionic gonadotropin levels as low as 25 mIU per ml, whereas the more complicated quantitative assay can detect levels as low as 5 mIU per ml. The latter assay can detect a pregnancy as early as 9 to 12 days after conception and possesses a reported sensitivity for ectopic pregnancy of nearly 100%; thus, a negative result excludes the diagnosis.

The development of commercial kits for both of these assays affords all clinical laboratories (licensed to use radioactive materials) the potential for providing these tests. The expensive reagents and laboratory equipment required, however, have precluded their universal availability. In addition, the need for reference standards that must be run with each test results in many of the laboratories running the specimens in batches; this causes varying delays in the reporting of results. The qualitative radioimmunoassay is widely available on the West Coast and is offered by most private and hospital-based laboratories; the radioreceptor assay is offered by 5% to 10% of hospital-based laboratories and relatively few of the private ones. For both of these assays, the time between receipt of the specimen in the laboratory and the results being reported back to the clinician is usually only a few hours and rarely as long as 24 hours. The quantitative radioimmunoassay is a very complicated assay with multiple reference standards and thus is run by most laboratories only once or twice a week.

Other Diagnostic Studies

Culdocentesis

Culdocentesis is a rapid and invaluable procedure in the evaluation of acute pelvic pain. By using this procedure it is possible to detect and to get a specimen of free intraperitoneal fluid in women. Hemoperitoneum, diagnosed when nonclotting blood is aspirated from the cul-de-sac, is present in 82% of cases of ectopic pregnancy; Berry and co-workers reported that the radioreceptor assay combined with culdocentesis detected 97% of cases of ectopic pregnancy. If clear or blood-tinged peritoneal fluid is obtained, the diagnosis of a ruptured ovarian cyst is substantiated. The diagnosis of pelvic inflammatory disease is supported by the presence of purulent fluid in the cul-de-sac, though other causes of peritonitis (ruptured appendix or ruptured diverticular abscess) can produce a similar finding. Culdocentesis is considered nondiagnostic if clotting blood or no fluid is aspirated.

Pelvic Ultrasonography

Pelvic ultrasonography can be an invaluable aid in diagnosing acute pelvic pain, especially in those patients with positive pregnancy tests. For example, the identification of an extrauterine gestational sac (found in only 15% of cases) leads to a definitive diagnosis of ectopic pregnancy. Conversely, the presence of an intrauterine gestation virtually excludes the possibility of an ectopic pregnancy because the two coexist very rarely (1 in 30,000 cases). Although most ultrasonographers accept the detection of a gestational sac within the uterus as sufficient evidence of an intrauterine gestation, it has been reported that this sonographic appearance can occasionally be simulated by the exfoliation of hyperplastic endometrium associated with ectopic pregnancy. For patients in whom the clinical

suggestion of ectopic pregnancy is high, some authorities thereby argue that an unequivocal diagnosis of an intrauterine pregnancy should not be made until either a fetal pole is identified or fetal heart activity is noted within the sac. Ultrasound studies can also be used to help substantiate the diagnosis in a patient suspected of having pelvic inflammatory disease by the finding of an inflammatory mass incorporating the uterus. In general, however, the sonographic appearances of the various pelvic conditions that can cause acute pelvic pain are frequently indistinguishable from one another and careful clinical correlation is required.

Examination of Endometrial Tissue

Although generally impractical, examination of the endometrial tissue in a pregnant patient who has acute pelvic pain becomes a feasible diagnostic option if the patient desires an abortion. The presence of chronic villi on microscopic examination of the intrauterine contents virtually excludes the diagnosis of ectopic pregnancy whereas the absence of such villi would identify a patient at high risk for an ectopic gestation.

Diagnostic Laparoscopy

The role of laparoscopy in the diagnosis of acute pelvic pain has been well established and it often negates the need for exploratory laparotomy. Although its routine usage in all but obvious cases of acute pelvic pain has been advocated, the risk-to-benefit ratio of such an approach has not been clearly established. It has been estimated that there are 4.6 major complications for every 1,000 laparoscopies done, with a death rate of 5.2 per 100,000. Nevertheless, diagnostic laparoscopy is clearly indicated in patients who have acute pelvic pain when the initial workup does not establish the diagnosis and there is a need to exclude life-threatening disorders such as ectopic pregnancy and acute appendicitis.

General Diagnostic Approach

The diagnostic approach to acute pelvic pain should begin with the determination of whether or not the pain is associated with a concomitant pregnancy. Although traditionally this distinction has been made on the basis of history or urine pregnancy tests, or both, a far greater diagnostic accuracy can be achieved by using one of the new commercially available serum pregnancy tests. For patients in whom the clinical suggestion of ectopic pregnancy is high, culdocentesis should generally be used in conjunction with pregnancy testing to more effectively exclude this diagnosis.

When a pregnancy test is positive in the setting of acute pelvic pain, the next vital step is to locate the tissue responsible for the human chorionic gonadotropin production. The finding of hemoperitoneum on culdocentesis confirms the diagnosis of ectopic pregnancy and denotes the need for immediate laparotomy. Pelvic ultrasound studies can effectively exclude the diagnosis of ectopic pregnancy by the finding of an intrauterine gestation or can confirm the diagnosis by identifying an extrauterine gestational sac. A positive pregnancy test in the absence of an intrauterine gestational sac on ultrasonography identifies a patient at particularly high risk for ectopic pregnancy, though other conditions can produce similar findings (for example, an intrauterine pregnancy too early to be identified by current ultrasonographic equipment or a recent spontaneous abortion with a pregnancy test that has not yet returned to negative). Depending on the clinical setting, numerous diagnostic options would be available including (1) expectant management with serial pelvic examinations, pelvic ultrasound studies or quantitative human chorionic gonadotropin measurements (or all three); (2) examination of the endometrial tissue, and (3) diagnostic laparoscopy. Gynecologic consultation should generally be obtained in such a clinical situation to aid in the decision-making process.

For patients who have acute pelvic pain in whom pregnancy has been excluded, the next helpful differentiation to be made is whether the pain is unilateral or bilateral. For patients who have unilateral pain, the principal considerations would be complications of an ovarian cyst, acute appendicitis and pelvic inflammatory disease. A diagnosis of adnexal torsion is substantiated by the finding of a tense, tender, cystic adnexal mass on examination, whereas a diagnosis of a ruptured cyst is confirmed by the aspiration of cyst fluid from the cul-de-sac. Acute appendicitis should be suspected in all patients with right-sided pelvic pain especially when associated with pronounced gastrointestinal symptoms and a low-grade fever. Although classically associated with bilateral pelvic pain, acute pelvic inflammatory disease is not an infrequent cause of acute unilateral pain and must be included in the differential diagnosis. Because the clinical diagnosis of pelvic inflammatory disease is frequently in error, an effort to substantiate with further studies should be routine, especially in cases that fail to present in a "classical fashion." Cervical Gram's stain, examination of the male partner, culdocentesis, pelvic ultrasound studies and diagnostic laparoscopy all have a role in confirming this diagnosis. Endometriosis, uterine leiomyoma and pelvic neoplasia are generally more likely to present as chronic pelvic pain. In cases of acute pelvic pain, these diagnoses are usually made on the basis of characteristic pelvic findings on examination or at diagnostic laparoscopy.

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Information

New Mexico's First Case of Plague

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THE FIRST CASE of plague in a human in the United States was reported from San Francisco in 1899.[1] From 1899 through 1926 California accounted for 80 percent (394/494) of human plague cases in the continental United States and the remainder occurred in other Pacific or Gulf Coast states (Florida, Louisiana, Texas, Washington).[2] Since 1927, however, plague cases have been more frequently reported from inland compared with coastal states. Thus, from 1949 through 1979, New Mexico (85 cases), Arizona (22), Colorado (13), Utah (3), Idaho (1), Nevada (1) and Wyoming (1) have together accounted for 85 percent (126/149) of the human plague cases in the American West.[2]

When a disease first appears in a geographic area, it may be difficult to recognize, especially if the disease is uncommon. The following narrative explains how plague, a disease new to the Southwest, was first diagnosed in New Mexico in 1949.

Report of a Case

DR POND: Near Cerro, in Taos County, a 9-year-old boy and his brother were returning from an unsuccessful rabbit hunt when the brother killed a prairie dog by hitting him in the head with a rock. Only a sick prairie dog could have been caught in this fashion. The other brother picked up the animal and they proceeded homeward. Nothing happened to the older brother, but the next day the 9-year-old boy became very ill and was brought to our office in Taos. He was seen by one of our associates and given penicillin for a presumed infected blister on his left hand, with lymphadenitis in the axillary nodes. He became much worse during the night and was taken to the Holy Cross Hospital (Taos) emergency room. He was promptly admitted to the hospital with a temperature over 40.6°C (105°F). I saw him the next morning. He had an angry red sore on his left hand and large, partially fluctuant nodes in the left axilla. There was little if any evidence of lymphangitis.

The boy appeared very sick and the thought of plague entered my mind. I had seen a case of plague in San Francisco in 1936. That patient was a veterinary surgeon, exposed constantly to animals and their fleas. He recovered in spite of a two- or three-day delay in establishing the diagnosis. As I questioned various experts about plague, I learned that the infestation of San Francisco had started with shipboard rats getting ashore. The wild rodents had become infected in turn. The experts also told me that the infestation in wild rodents would spread eastward and eventually involve New Mexico where I intended to practice. Consequently, when I moved to New Mexico later in 1936, I expected eventually to see a case of plague. In fact, before 1949 I had sent specimens on a couple of less suspicious cases to the state laboratory in Albuquerque for plague testing and always received negative reports. The laboratory accused me of crying wolf.

I aspirated the 9-year-old boy's bubo and a direct smear showed an organism that could well be *Yersinia pestis*. The rest of the material was cultured and injected into guinea pigs. The following day I was called to the biological laboratory, to be greeted by several dead guinea pigs alongside microscopes with smears of the deadly plague bacillus. Up to this point I had still thought of plague as a farfetched diagnosis. I suddenly realized that it was here and now. Not fully appreciating the role of fleas, I began to worry about my own exposure to this deadly bug. Perhaps a little *snakebite medicine* relieved some of the worry.

The state laboratory met the plane with a sample from the patient's axillary bubo. They kindly reported a suspicious smear by phone and the next day had a positive diagnosis with their guinea pigs. In the meantime I wired San Francisco for an update on antibiotic treatment of plague. The answer was to use a combination of streptomycin and sulfadiazine. A regimen of these was started immediately; the boy began to improve almost at once and in a couple of days he was well on the way to an uneventful recovery. This was the first case of plague in New Mexico.

Comment

Plague infection in animals in this country appears to have started at the end of the 19th century and the beginning of the 20th century when rat plague appeared in port cities on the Pacific Coast.[1-4] Then, plague apparently invaded wild rodent populations close to port areas (first documented in California in 1908).[1] Once established in sylvatic rodents, plague spread rapidly to rodent populations throughout large areas of the West,[1-4] as documented by US Public Health Service surveys conducted in the 1930s and 1940s.[1] The plague expert's prediction that wild rodent plague would reach areas like New Mexico was confirmed in 1938 when it was found in rock squirrels *(Spermophilus varie-*

Refer to: Pond A III, Mann JM: New Mexico's first case of plague (Information). West J Med 1983 Jul; 139:114-116.

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gatus) and prairie dogs *(Cynomys gunnisoni)* in Catron County.[1]

Report of this first New Mexico plague case, with the attendant publicity, probably facilitated recognition of two subsequent but unrelated plague cases in New Mexico in 1949. From 1949 through 1982, a total of 114 cases with 22 fatalities were reported from New Mexico. Recognizing a rare disease is always a difficult accomplishment; consideration of plague in New Mexico and in other western states remains a challenge.[5,6]

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Newer Forms of Insulin

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THE PURITY of insulin has changed dramatically in the past ten years and indications for the use of the newer and more purified forms are being established. There are now 42 insulin products in the United States, and at least six more products for human use will probably be approved soon by the Food and Drug Administration (FDA).

The term "purified insulin" is somewhat misleading because as each new purification step was adopted for use in commercial preparation of insulins, the product was described as "purified." Current FDA terminology, however, allows only insulins containing less than 10 ppm of proinsulin and other related residues to be called purified insulin. These insulins became available in the United States in 1980 and were an improvement over the conventional insulins, which contained up to 30,000 ppm of impurities.

The purified insulins are made from either beef or pork insulin, as are the standard insulins, though many of the standard insulins are combinations of both. Immunogenically, pork is preferable as an insulin source because only 1 of the 51 amino acids making up the insulin molecule is different from that in the human insulin molecule, compared with three different amino acids of the beef insulin molecule. The species differ enough immunologically to cause greater antibody formation in those persons exposed to purified beef insulin than in those treated with purified pork insulin.

Refer to: Bohannon NJV: Newer forms of insulin (Information). West J Med 1983 Jul; 139:115-116.

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In the United States insulins now range in purity from 50 ppm to less than 10 ppm, with the purified insulins available only in concentrations of U 500 (500 units per ml) (for insulin-resistant states) and U 100. Other insulins can be obtained in U 40 concentrations, and insulin diluents are available for mixing concentrations that may be desired for use in insulin pumps or for making small doses such as for infants.

The indications for use of purified insulins are as follows:

- *Lipoatrophy* (pitting at the insulin injection site). This complication disappears when a patient is switched to purified pork insulin. Administration of purified insulin must be continued after resolution of the lipoatrophy, however, because reexposure to the less pure insulin, even though at a different injection site, can cause a reappearance of the atrophy that is resistant to subsequent treatment with the more purified forms. An immune component of lipoatrophy is suggested by the high coincidence of local allergy and lipoatrophy (15 percent) and the reduction of the atrophy with local injection of steroids.[1]
- *Insulin hypertrophy* (fat hypertrophy at injection site). This complication may also have an immune component. It does not respond as predictably to therapy with purified insulins, however, with improvement occurring in only about half of the patients.[2]
- *Allergic reactions to insulin.* Allergic reactions take several forms. Local allergic responses to insulin are varied and can occur within 15 minutes to 2 hours after the injection or they can be delayed and not appear for 4 hours or more after the injection. Common allergies often occur one to four weeks after institution of insulin therapy or within a few days of reinstitution of insulin and are characterized by a hard, red induration at the injection site. The longer acting insulins are more likely to induce this response. Protamine, the agent that slows the action of isophane insulin suspension (NPH insulin), is itself a significant antigen. Systemic allergic responses can also occur and are characterized by urticaria or angioedema, or both, which is mediated by IgE antibodies. More than 60 percent of persons having systemic allergic reactions to insulin have had intermittent insulin therapy and 37 percent are allergic to penicillin. Systemic allergic reactions to insulin are potentially life threatening. If continuing insulin therapy is necessary, a patient should be desensitized in hospital using purified insulins according to the protocol accompanying the desensitization kit, and then maintenance doses of insulin must be administered to maintain the desensitization.
- *Antibody-mediated resistance to insulin.* Such resistance occurs equally in both sexes and usually appears within five years of institution of therapy (in 66 percent of these, insulin resistance develops within the first year). Onset is usually gradual and 75 percent of insulin-resistant patients are older than 40 years of age. About half of these patients need more than 1,000 units of insulin a day and occasionally more than 25,000 units a day is needed during a resistant phase.

Insulin resistance is usually self-limited and spontaneously resolves in six months to a year.[3] Treatment with systemic steroids usually leads to abatement of insulin resistance in a few days but often releases previously antibody-bound insulin and therefore may precipitate hypoglycemia. Use of purified insulins in diabetic patients is expected to decrease the incidence of antibody-mediated insulin resistance.

• *A newly diagnosed case of diabetes.* Development of insulin antibodies is influenced by several factors, among which are species specificity (beef is more antigenic than pork), the physical state of the insulin preparation (modified insulins are more antigenic than regular or fast-acting insulins) and purity. The differences in chemical structures among porcine, bovine and human proinsulin are much greater than the differences among their insulin molecules; thus, contamination with proinsulin may lead to development of cross-reacting antibodies that bind to insulins. In newly diagnosed diabetic patients who have been treated with purified pork insulin for one to two years, insulin antibodies developed in only 10 percent, compared with 75 percent of patients treated with conventional pork insulin for one to two years.[4] For this reason many diabetologists believe that all patients being started on insulin therapy for the first time should be treated with purified insulins. Other evidence[5] suggests that more C-peptide (and insulin) secretory capacity may be preserved in new patients treated with purified insulin compared with those treated with conventional insulins.

• *Pregnancy is present or contemplated.* Conventional insulin treatment before pregnancy influences insulin antibody levels that will be present during pregnancy. Insulin antibodies freely pass to the fetus and may be related to neonatal morbidity. Switching to purified pork insulin during pregnancy produces significant falls in insulin antibody levels.[6]

• *Short-term or intermittent insulin therapy.* Patients in whom short-term or intermittent insulin therapy is anticipated (that is, gestational diabetic women or acutely stressed type II diabetic persons) should be treated with purified insulin to minimize antibody formation and possible development of insulin allergy or insulin resistance.

Although it seems unlikely that the development of complications of diabetes would be affected by the purity of the insulin per se, the purity may affect development of complications indirectly by affecting the degree of control of diabetes. Insulin that is bound by antibodies is not immediately available to the cells and may lead to a later peak action of insulin preparations and a longer duration of insulin action. Thus, adjustments made to quickly correct hyperglycemia by using fast-acting insulins may not be so successful when large amounts of antibody are present.

Finally, although it would be desirable for all patients treated with insulin to be receiving purified preparations, the added expense is significant. Purification is the most costly step in insulin production, and for this reason biosynthetic human insulin produced using recombinant DNA technology or chemical modification of pork insulin cannot be expected to lessen the cost. Purified insulins cost about $4.50 to $7 more per vial than conventional insulins in community pharmacies. Many patients are unwilling or unable to bear this added expense.

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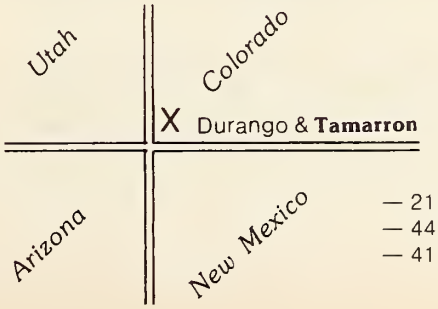

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

DIGESTIVE DISEASES—Editors: John T. Galambos, MD, Professor of Medicine; Director, Division of Digestive Diseases, Emory University School of Medicine, Atlanta; and Theodore Hersh, MD, Professor, Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine. Butterworths, 10 Tower Office Park, Woburn, MA 01801, 1983. 701 pages, $49.95.

The editors were assisted by the faculty of the Emory University School of Medicine in writing a practical handbook of clinical gastroenterology. Its stated goal is to help physicians in patient care. It is organized in two parts. Part one deals with common gastrointestinal symptoms and abnormal physical and laboratory findings. Part two deals with specific disease entities. There is an appendix on radiology.

The topics are covered in a commonsense manner. The discussions are quite superficial: lean on physiology but heavy on opinion as to how to approach the problems posed. This opinion is derived from the "clinical experience" of the authors. There are very few literature citations. The quality of the chapters is variable as one would expect from a multiauthored work. Those by Dr Galambos on liver disease are quite good; the remainder less so. The topics are selected; there are notable omissions. There is no consideration of carcinoma of the esophagus, stomach or small bowel. The proofreading was poor. Laboratory function tests are under the heading of physical examination. In the section on anorectal disease, there is a subsection on miscellaneous oral (anal?) diseases.

I cannot recommend this book for its targeted audience of primary care physicians, consultants, house officers and students. There are large gaps in the topics covered. The diagnostic and therapeutic recommendations are opinionated and do not discuss reasonable options. The treatment of the subject matter is frequently superficial, but this may be because of the space limitations imposed by a handbook.

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DIAGNOSIS AND MANAGEMENT OF PERIPHERAL VASCULAR DISEASE—Editor: D. Craig Miller, MD; Associate Editor: Anthony J. Roon, MD; Series Editor: Donald C. Harrison, MD; Foreword by Norman E. Shumway, MD, PhD. Addison-Wesley Publishing Company, Inc, Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA 94025, 1982. 314 pages, $34.95.

The volume of literature on clinical vascular disease related topics has expanded enormously in the last five years with both comprehensive texts that address the entire field and those that specifically address individual topics such as noninvasive diagnosis, aneurysm surgical procedures and cerebrovascular disease. In large measure, these have been directed toward practicing vascular surgeons and yet many of the clinical advances in the field in both diagnosis and treatment have not yet been appreciated by primary care physicians, while students are so overwhelmed by the sheer volume of facts in such texts that they too have difficulty in determining what is clinically relevant.

The editors have addressed this need by compiling a relatively short, easily readable monograph that covers the areas of vascular disease of greatest clinical relevance. The choice of authors for the individual chapters is appropriate in that all are contributors of considerable stature, and each provides a basic, concise and yet informative review of clinical vascular disease topics.

The sequence of chapters in the initial portion of the book is well designed to provide the reader with a logical progression from history and physical examination through the various noninvasive and invasive diagnostic techniques and the chapters on arteriographic techniques in particular are well presented and well illustrated. The organization of the remaining chapters would have been improved by a closer grouping of topics dealing with similar or related diseases, as for example could have been accomplished by grouping the discussion on chronic arterial insufficiency of the lower extremities with those on acute arterial insufficiency and atheroembolism. This would then have provided a more logical progression of the chapters on aortic diseases without interposing those on cerebrovascular and thoracic outlet problems. These issues, however, are largely a matter of style and are not serious deficiencies.

The organization of individual chapters facilitates recognition of the important aspects of the condition being discussed although for the audience to whom this is projected, a more uniform approach in each chapter may have improved the comprehension. For example, a discussion of the natural history of each of the individual topics would enable the reader to focus more sharply on the merits of surgical intervention. The value of such an approach is best appreciated in the chapter on lower extremity occlusive disease which provides the reader with a clear appreciation of the relative unimportance of intermittent claudication with regard to limb loss while stressing the value of this symptom complex in identifying a patient population at risk from the complications of generalized atherosclerosis. Against this background, the role of surgical therapy has been clearly outlined. In a similar manner, the chapter on venous thromboembolic disease provides the reader with a lucid understanding of these conditions with an equally clear discussion of treatment options. The absence of this approach in all chapters is responsible for the impression that the text is written predominantly by surgeons (which it is) and will probably result in both students and internists alike, to whom the book is primarily directed, concluding incorrectly that only the surgical side of the story is presented.

The introductory chapter on history and physical examination suffers from providing pathologic and epidemiological data in the midst of physical examination methods, which tends to divert the reader's attention from the otherwise well-described techniques. For example, when the diagnosis of abdominal aortic aneurysms is discussed, the authors incorrectly state that the majority of aneurysms are symptomatic (perhaps an editorial error) but then discuss a number of unusual complications without stressing that rupture is by far the most frequent. Because such factors are well covered in later chapters, for the sake of clarity this type of information would have been best deleted from this section. Unfortunately, a number of spelling errors throughout the text also detract from the overall appeal.

In the main, however, the content of chapters is well organized and clear. Each is complemented by a comprehensive but not exhausting list of appropriate references, and in spite of the relatively minor criticisms already noted, the authors are to be congratulated for compiling an informative, introductory text on peripheral vascular disease, the necessity for which has existed for too long.

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Original Clinical Articles

Sleep Apnea: A Prospective Study

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Sleep apnea is remarkably prevalent among general medical patients. Of 26 men randomly selected on a Veterans Administration hospital medical ward, with a mean age of 66.2 (SD=11.5) years, 7 (27%) had sleep apnea. Of concern is that two of the seven patients were receiving hypnotic drugs. Portable sleep recordings may need to be done when routinely assessing elderly medical patients.

In recent years a growing number of investigators have described large clinical case series of patients who have sleep apnea.[1,2] Nevertheless, many physicians still regard it as a rarity.

Findings from several studies have suggested that sleep apnea may indeed be highly prevalent among older persons. Webb[3] reported that sleep apnea was caused by changes in the central nervous system and that age heightened these changes. Block and co-workers[4,5] found that sleep apnea was positively correlated with increasing age in both men and women. Reynolds and associates[6] reported that of the elderly patients seen in their clinic because of sleep disturbances, 18.5% had sleep apnea. Most of these studies, however, describe patients from sleep disorder clinics. Two separate groups have studied population samples from senior citizen clubs. Carskadon and Dement[7] selected seniors who stated they were in good health and did not have sleep problems. Remarkably, 37% of these persons had sleep apnea syndrome, largely central sleep apnea. Ancoli-Israel and colleagues[8] selected seniors who had symptoms related to sleep. The same percentage—37%—was found to have sleep apnea syndrome, but a much larger percentage of these subjects had mixed or obstructive apnea, and 37% also had periodic movements during sleep (leg jerks).

Because many inpatients are older,[9] we became interested in the question of how often sleep apnea presents in a general clinical setting. To explore this question, we surveyed randomly selected patients on a medical ward.

Patients and Methods

Patients

Our study comprised 26 men, with a mean age of 66.2 years (±11.5; range, 38 to 88). The subjects were volunteers from a general medical service in a Veterans Administration (VA) Medical Center. The service is an academic teaching service with a high turnover; the average stay of patients is eight days.

House officers were consulted as to which patients from each day's admission list were too medically unstable or demented to participate. Patients expected to be discharged within three days of admission were also excluded. The patients excluded made up 45% of all the patients admitted during the study, a period of three months. Candidates were randomly selected from the remaining 55%, and each was asked to volunteer for the study.

Apparatus

A Medilog four-channel portable recorder was used to record sleep.[10] Two channels recorded thoracic and abdominal respiration by means of Respitrace transducers.[11] A third channel summed electromyographic signals from the musculus tibialis anterior of both legs. The fourth channel recorded dominant wrist activity. These four-channel recordings allowed analysis of wake and sleep, number and duration of apneic episodes and number of leg jerks.*

Procedure

Each subject gave a full sleep history and a brief medical history. Each was then hooked up to a recorder for one night (mean, 15 hours). All recordings were done at a patient's hospital bed on his own ward. To allow a patient's sleep to adjust to the hospital environment, each recording was done between the third and seventh day of hospital stay. Each patient was also asked to subjectively evaluate his sleep the morning following the recording. Because the recording equip-

*Mr William Mason provided technical assistance.

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Submitted, revised, October 28, 1982.
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TABLE 1.—*Characteristics of 43 Men Selected for Study*

Patients Asked to Participate	*Number*	*Mean Age (SD)*	*Patients With COPD Number*
Recorded	26	66.2 (11.50)	3
Dropped out	2	60.0 (1.41)	2
Refused recording	15	65.5 (14.65)	4

SD = standard deviation; COPD = chronic obstructive pulmonary disease.

TABLE 2.—*Description of Sleep Apnea in Seven Male Patients*

Subject	*Age*	*Episodes of Apnea Number*	*Duration of Longest Apnea (sec)*	*Type of Apnea*
1	55	41	28	Central
2	59	46	22	Central
3	88	56	20	Central
4	73	86	36	Central
5	63	200	54	Mixed
6	71	298	27	Mixed
7	74	311	24	Mixed

ment is portable, each patient was completely ambulatory. This minimized changes in a patient's routine and minimally interfered with that person's normal sleep patterns.

The sleep records were evaluated for the presence or absence of sleep apnea and nocturnal myoclonus. Sleep apnea was diagnosed when there were 30 or more episodes of apnea observed during sleep, each of at least ten seconds' duration. In addition, the apnea index (the number of occurrences of sleep apnea per hour of sleep) had to equal or exceed 5.0. For the patient's benefit, diagnostic findings were reported to medical staff.

Results

Patient Selection

In all, 43 male patients were asked to give informed consent for the study under procedures approved by the VA Committee on Human Subjects. (Patients in the VA Medical Center are primarily men; therefore, we were unable to include women.) Of the 43 patients who were asked to participate, 15 refused. Of the 28 patients who consented, 2 suffered exacerbations of preexisting dyspnea during the recordings and requested to have the apparatus removed. Subsequent follow-up showed that the dyspnea was unrelated to the recording apparatus. In all, 26 recordings were completed without incident or adverse effects. There seemed to be a trend (P less than .06) for patients with chronic obstructive pulmonary disease to refuse consent or to drop out of the study. There were no significant differences in the ages of the patients recorded and those refusing consent (see Table 1).

Medical History

None of the patients had had sleep apnea previously diagnosed nor had sleep apnea been suspected by prior medical evaluations. Of note is that 11 of the patients (42%) recorded had been admitted for cardiac-related problems.

Sleep Disorders Results

Of the 26 patients recorded, 7 (27%) were found to have sleep apnea—that is, more than 30 episodes of apnea per night and an apnea index equal to or greater than 5.0. Three additional patients (11.5%) had 24 to 27 episodes of apnea, thus almost meeting criteria. None of the patients had nocturnal myoclonus.

Characteristics of the patients with sleep apnea are shown in Table 2. The mean age of the seven apneic patients was 69.0 ± 11.09 years (range, 55 to 88 years of age). The mean age of the nonapneic patients was 62.5 ± 11.36 years (range, 38 to 88 years of age). There was no significant difference in age between the two groups. The three patients who had 200 or more episodes of apnea per night had mixed, but largely obstructive, apnea. The other four patients had central sleep apnea.

Associations between sleep apnea and various other characteristics of the patients were examined with the Fisher's exact probability test. Congestive heart failure was significantly more prevalent in the apneic group than in the nonapneic group (P less than .05). Higher incidences of hypertension, diuretic use, myocardial infarction, angina, snoring and morning drowsiness were also noted in the apneic group, but these associations were not significant. Chronic obstructive pulmonary disease was less prevalent among the apneic patients, but this again was not significant. No associations were found with insomnia complaints, elevated hematocrit or use of sleeping pills.

Discussion

This study shows that sleep apnea is remarkably prevalent among elderly patients on a medical ward. Seven (27%) of our medical patients had sleep apnea. Three patients (11.5%) had a moderately severe form, having more than 200 episodes of apnea per night. Our study patients were somewhat older than the national average of medical inpatients,[9] however, which might explain the relatively high prevalence among them. In addition, in excluding those patients who were acutely ill or demented, we possibly excluded those who had sleep apnea. Although patients who had chronic obstructive pulmonary disease were reluctant to participate in the study, we found little evidence of apnea among them. Also, the patients with sleep apnea had significantly more congestive heart failure than the patients with no sleep apnea. Further studies are needed to determine the causal relationship between these two disorders.

Exact percentages of patients who have sleep apnea will vary from hospital to hospital. As mentioned, although our subjects were inpatients, they were also predominantly elderly and so our results support other findings that sleep apnea is prevalent among older persons.[3-8] Of course, this age group makes up a substantive percentage of all hospital patients. The results of our study highlight the importance of examining sleep apnea in general medical settings.

It is interesting that despite efforts our sleep clinic

has made to educate our colleagues, and despite the heightened interest produced by our ongoing survey, our medical service did not suspect sleep apnea in any of these patients before our recordings. If failure to recognize sleep apnea occurs in an informed academic setting, much the same failure could occur elsewhere. It is of particular concern that two of our seven apnea patients received hypnotic drugs, though these respiratory depressants could be expected to worsen sleep apnea.[12] The widespread use of hypnotics on medical wards must be rigorously questioned if sleep apnea is so common.

Our portable recording technique proved extremely practical and convenient. Although we did not record oxygen saturation levels, the portable recorder does allow for clinical screening. Because it is clearly difficult to make a diagnosis of sleep apnea based on history alone, we believe that, like electrocardiograms, portable recordings for sleep apnea deserve a place in the routine assessment and screening of elderly medical patients.

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Articles to Read in Other Journals

The Cutaneous Manifestations of Diabetes Mellitus
Huntley AC
Journal of the American Academy of Dermatology
7:427-455, Oct 1982
DISCIPLINES: Dermatology, Internal Medicine, Family Practice
READABILITY: Good

This is an extensive review that supplies the reader with essentially all the information on the cutaneous changes and markers for diabetes. It should be of value to all physicians who are involved with the diagnosis and care of patients with diabetes.

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Rehabilitation Aspects of Human Sexuality

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The PLISSIT model is a comprehensive program that combines educational strategies with behavioral intervention to integrate human sexuality into the initial rehabilitation of spinal cord-injured persons. Sexuality is treated as a health care issue as important as bowel and bladder care, skin care, psychosocial issues, mobility, self-care and vocational concerns. Patients admitted to the Spinal Cord Injury Program are surrounded by a supportive milieu and an interdisciplinary staff who comfortably incorporate sexuality into discussions about catheter care, positioning, communication styles, assistive devices and so forth. Patients are exposed to a behavioral training program that makes available didactic lectures, group and individual sessions, bibliotherapy, films and opportunities for directed overnight sexual exploration within the hospital. We advocate that sex therapy be integrated into comprehensive rehabilitation programs along with physical therapy, occupational therapy, recreation therapy and psychotherapy as an integral and effective form of functional restoration for patients with major physical disabilities.

The blossoming of effective techniques for treating sexual dysfunctions in healthy persons[1,2] can have tremendous impact on the management of spinal cord-injured patients. At Casa Colina Hospital for Rehabilitative Medicine an organized program of sexual rehabilitation has been developed for recently disabled persons. Modern sex education, counseling and therapy techniques have been systematically integrated into the initial comprehensive rehabilitation plan for newly paraplegic and quadriplegic persons.

Statement of Beliefs

We believe, first, that sexual functioning is a legitimate and important concern in a comprehensive rehabilitation program. Second, as in the areas of atrophy, contractures and decubitus, early intervention maximizes function and minimizes secondary complications. Third, the PLISSIT model of sex therapy (described in the following section) provides the opportunity for involvement of all staff and patients according to their interest and level of comfort.

Treatment Model

The PLISSIT model[3,4] is based on a vertical structure of emphasis in sex therapy beginning with *P*ermission and proceeding through *L*imited *I*nformation, *S*pecific *S*uggestions and *I*ntensive *T*herapy (see Figure 1). The model is both flexible and comprehensive and provides a framework for differentiating those problems amenable to brief treatment approaches from others requiring intensive therapy.

Permission

We have found that permission is most effective when it is consistently reflected by authority figures, treatment staff and peers. The topic of sexuality is introduced by a physician within hours of a patient's admission to the rehabilitation center while taking an overall medical history and doing a physical examination. The nature of current intimate relationships is assessed, premorbid sexual patterns are reviewed and a history obtained regarding the patient's awareness of sexual feelings, erection, ejaculation and orgasm since the acute injury. The genitalia, sacral sensation, voluntary rectal control and the sacral reflex arc are examined. The relationship of these findings to sexual potential is explained and the patient is given suggestions to further explore and become aware of his or her newly changed body. The patient is oriented to the presence within the hospital of the Activities of Daily Living Apartment, which provides an opportunity for privacy and for sexual exploration. Thus permission is granted by the physician for sexuality to be a very matter-of-fact and routine aspect of the rehabilitation process.

Because the total treatment milieu represents a vital force in shaping patients' acceptance and risk taking,

Refer to: Madorsky JGB, Dixon TP: Rehabilitation aspects of human sexuality. West J Med 1983 Aug; 139:174-176.

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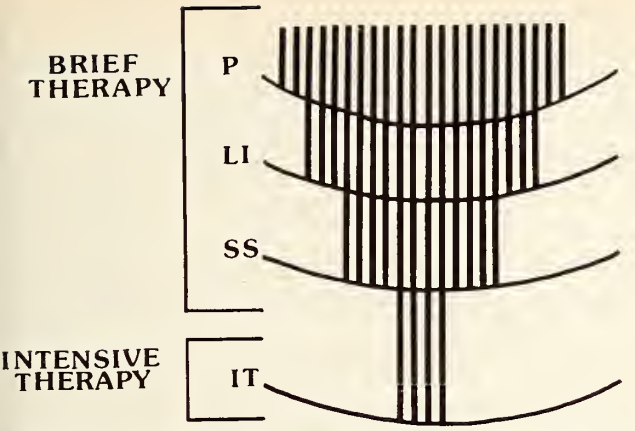

Figure 1.—The PLISSIT model provides four levels of approach to the treatment of sexual concerns: Permission (P), Limited Information (LI), Specific Suggestions (SS) and Intensive Therapy (IT). The first three levels can be viewed as brief therapy, the fourth level as intensive therapy. Most sexual concerns can be treated with the briefer approaches (adapted from Annon[3]).

all members of the staff are encouraged to reflect permission and to be tolerant and supportive of the expression of concerns related to sexuality. All staff members have been encouraged to explore their own attitudes and personal comfort levels by participating in a Disability Sexual Attitude Reassessment Workshop.[5] It is recognized that staff members, patients, spouses and "significant others" vary in their openness, interest and degree of concern about sexuality. We therefore strive for an approach that is sensitive to the range of individual needs and values.

Limited Information

In addition to a commitment to permit dealing with sexual issues, interested members of all team disciplines are developing an expertise as educators in sexual functioning as it relates to their own area of responsibility. For example, a physical therapist might discuss and teach aspects of bed mobility and positioning as it relates to sexual activity; an occupational therapist might extend alternate ways of functioning and the use of adaptive equipment to the sexual sphere, and members of nursing staff teach coping skills related to involuntary bowel movements and bladder incontinence during a potential sexual interaction. In group educational sessions information is transmitted regarding male and female anatomy and physiology, and the effect of spinal cord injury on sexual response cycles, fertility and methods of contraception. Patients and family members may also be referred to books, articles and videotapes available in the patient library.

Specific Suggestions

A psychologist and a social worker meet regularly with a patient and spouse or significant other, if available, to evaluate in greater detail their personal strengths, their level of adjustment to the disability and the viability of the relationship. As part of the psychosocial evaluation, a premorbid sexual history of both partners may be obtained. This is of special importance because recently published findings indicate that 40% of healthy men and 63% of healthy women who are happily married suffer from erectile or orgasmic dysfunction.[6] Private and group counseling sessions are designed to broaden attitudes regarding the scope of sexuality, decrease anxiety about performance and increase ability to communicate effectively about sexual issues. Topics such as self-stimulation, fantasy and sexual myths about able-bodied and disabled men and women are discussed. Sexually explicit movies may be used to provide further material for discussion. Previously discharged male and female spinal cord-injured patients are invited to the group sessions and act as peer counselors. Specific suggestions that emerge may be as concrete as to empty the bladder before sex play to decrease anxiety over bladder incontinence, to adjust the timing of antispasticity medications if they seem to impede erections or to use assertive communication skills in social and sexual interactions.

Intensive Therapy

Intensive therapy is individually designed for each patient or couple by the psychologist and physician who work in close cooperation and on occasion as a cotherapy team. Individual and, if appropriate, couple exercises are assigned to be carried out in the Activities of Daily Living Apartment or at home while on leave from hospital. Sensate-focus exercises serve to increase awareness of one's own sexual responses and to alleviate performance concerns. Exercises also help to structure time to focus on resolving sexual problems and to promote new forms of verbal and nonverbal communication. For those patients without a sexual partner, individual sensate-focus exercises and social skills training exercises may be assigned. These patients are given opportunities to try out social skills on recreational trips away from hospital. Patients or couples return on a regular basis to counselors to review experiences, to explore their emotional reactions and to receive new assignments.

Report of a Case

The sexual rehabilitation process is exemplified by the case of a 21-year-old man who suffered a C5-6 fracture dislocation in an automobile accident. He immediately became quadriplegic and had complete loss of strength and partial sensory sparing below C6. At the time of admission to Casa Colina Hospital for Rehabilitative Medicine several weeks after injury, sacral sensation was present but diminished, voluntary anal sphincter control was absent and bulbocavernous and anocutaneous reflexes were hypoactive. The patient indicated that he had genital sensation and had experienced erection when his external catheter was applied. He related that he had asked his neurosurgeon regarding his prognosis and had been told that he would never be able to have sex again. The patient was then informed that many spinal cord-injured men are able to have satisfying sexual relationships. He was encouraged

to get to know his body as it now is and to explore it in terms of areas of pleasant sensation, diminished sensation, dysesthesia and absent sensation.

About two weeks after admission, the patient met with his physiatrist (J.B.M.) to discuss aspects of his management. He described his experiences with self-exploration since being admitted to hospital. He was further informed and reassured regarding the sexual capacities of spinal cord-injured men. He was eager to further explore his sexual capacities.

A meeting was then held with the young woman with whom the patient was intending to live following discharge. She wanted very much to spend the night with him. She felt that she was in love with him, but feared that if things did not work out sexually, the relationship would be doomed. She was given basic information, reassurance regarding the normalcy of her concerns and permission to take care of her own needs as well as his.

Six weeks into the rehabilitation program, the couple stayed overnight in the Activities of Daily Living Apartment. Afterwards the patient reported that he had been preoccupied with when to remove his external catheter and how often to put it back on. He was pleased that he did not wet the bed, had no involuntary bowel movements and remembered to turn so as to prevent decubitus ulcers. His partner had been worried about losing the spontaneity of sex and concerned that having to assist the patient physically would detract from the romance of the moment. Nonetheless, she experienced orgasm for the first time in her life, following oral stimulation by the patient. They also had successful intercourse but without ejaculation or orgasm for him. After several more sessions in the Activities of Daily Living Apartment, the patient was reporting occasional orgasm and ejaculation. His ability to feel sensations in his genital area was much less intense than before the accident, but his erections lasted indefinitely, as long as stimulation continued. After ejaculation, continued stimulation led to several orgasms in a row. His partner was elated because she was now regularly orgasmic with the patient. They had some questions about their prospects for having a child and a semen analysis was recommended.

After 18 weeks the patient was ready for discharge. He had reached his goals in mobility, self-care, bowel and bladder management, and psychological and vocational rehabilitation.

Since discharge about a year ago, the couple has been seen several times in follow-up. They are both working and they continue to have a good sexual relationship. They feel that the opportunities they had for sexual exploration during his hospital stay strengthened their relationship and contributed to his overall positive attitude about himself and to his success in the total rehabilitation program.

Discussion

It was not until the decade of the 1970s that significant attention was paid to sexual rehabilitation for patients with physical disabilities. This occurred despite findings that spinal cord-injured patients who were sexually dysfunctional also lacked motivation for vocational rehabilitation,[7] an impression that patients who avoid dealing with their sexuality also avoid realistic acceptance of their disability[8] and data that sexual problems rank high in importance for many spinal cord-injured patients.[9]

Since the 1970s there has been a blossoming of sex education and counseling programs,[10-14] but there continues to exist a subtle and sometimes overt belief that sex therapy is for "old" cord-injured patients. The myth is that recently injured patients are not ready for sexual rehabilitation. Certainly Maslow's hierachy of needs[15] would suggest that concerns for survival are more basic than a concern for sexuality; once the life and death issues are settled, however, and a patient is sufficiently medically stable for comprehensive rehabilitation, we believe he or she may also be ready to deal with sexual issues. We ascribe to cognitive social learning theory ideas that suggest that the expectancies and beliefs held by authority and staff will significantly affect the beliefs of persons living in the environment. Acute spinal cord-injured patients will rarely be comfortable addressing the issue of their sexuality as long as the milieu they live in is uncomfortable about this topic or believes it is too early to address it. We agree with Griffith and Trieschmann[16] that early active intervention and the availability of a private area within hospital for sexual exploration are highly beneficial.

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Intestinal Parasitic Infections in Homosexual Men at a San Francisco Health Fair

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In a sample of homosexual men attending a San Francisco Bay Area health fair, there were strikingly higher prevalence rates of intestinal parasitic infections compared with rates in a control group of health plan members who had a routine multiphasic health examination. Physicians treating homosexual men must be aware of the likelihood of such infections, whether or not the patients are symptomatic.

For the past several years, we have been engaged in a survey of intestinal parasitic infections among homosexual men in the San Francisco Bay Area. Participants in this continuing survey to be described in a subsequent report are drawn from a number of community organizations. Recently we took part in a health fair organized by the Bay Area Physicians for Human Rights (BAPHR). BAPHR's predominantly gay membership of 360 physicians seeks to promote greater understanding of the medical problems of homosexuals. We are most grateful to the group for having allowed us to join them in the health fair, which took place in San Francisco on April 24 and 25, 1982.

Although attendance at the fair was not restricted to homosexuals and heterosexual participation was encouraged, the health fair planning committee of BAPHR physicians, working with other community health professionals, organized diagnostic and informational services that targeted suspected medical risks of a homosexual population. By making use of extensive publicity in local gay newspapers and leaflets distributed in the predominantly homosexual neighborhoods of San Francisco (including the Castro district, where the testing facility was located), the fair attracted some 650 participants, of whom about 67% were gay men. Through prior arrangement, the intake workers, all of whom were BAPHR physicians, advised all homosexual men to undergo stool specimen examination for parasites. The testing was urged regardless of whether or not the intake interview turned up gastrointestinal symptoms or the volunteer had a history of such problems.

At the intestinal parasite station, kits were distributed to all health fair participants who, after an explanation of the aims and procedures of the study, requested testing. A total of 180 testing kits were distributed before supplies ran out and 105 volunteers returned specimens for analysis in the three-week period after the health fair during which they could be accepted. Each volunteer was given two vials containing a combination fixative-preservative solution of polyvinyl alcohol and mercuric chloride and directions for processing stool specimens obtained on two separate days. Each was also asked to complete a questionnaire recording age, race, past history of certain sexually transmitted diseases, the presence or absence of certain symptoms that may be related to parasitic disease and a number of factors relating to intensity of exposure. The questionnaires were identical to those being used in the areawide survey, and much of the information they elicited awaits statistical analysis upon conclusion of that study.

We received completed questionnaires from 103 of the 105 persons submitting stool specimens. One respondent whose questionnaire was otherwise complete did not state his age. Racial distribution was as follows: Asian, 2; black, 3; Hispanic, 3; white, 95. Age distribution by decade was 21 through 30 years, 24; 31 through 40 years, 47; 41 through 50 years, 19; 51 through 60 years, 11, and 61 through 70 years, 1.

The prevalence rates of the intestinal protozoans found in the group sampled are compared in Table 1 with those found in a control group of 415 San Francisco Bay Area persons who had a routine multiphasic health examination at the Kaiser-Permanente Medical Center in Oakland, California.[1] The number of specimens examined and the method of examination were

Refer to: Markell EK, Havens RF, Kuritsubo RA: Intestinal parasitic infections in homosexual men at a San Francisco health fair. West J Med 1983 Aug; 139:177-178.

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Submitted, revised, October 7, 1982.

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Reprint requests to Edward K. Markell, PhD, MD, Department of Internal Medicine, Kaiser-Permanente Medical Center, 280 W. MacArthur Boulevard, Oakland, CA 94611.

TABLE 1.—*Prevalence of Intestinal Protozoa in Gay Men and in the General Population of San Francisco*

Parasite	Percent Infected	
	Health Fair (N=105)	*Multiphasic* (N=415)*
Any	59.1	14.2
Potential pathogen	31.4	5.5
Entamoeba histolytica	26.7	0.7
Entamoeba hartmanni	24.7	1.9
Entamoeba coli	17.1	3.6
Endolimax nana	38.1	6.5
Iodamoeba bütschlii	18.1	1.2
Dientamoeba fragilis	1.0	3.1
Giardia lamblia	4.8	1.7

*Multiphasic health examination group=415 persons.

the same in both groups. As only two stool specimen examinations were done for each person in both groups studied, the actual prevalence rates are probably higher in both groups.

The prevalence for *Entamoeba histolytica* was similar to that noted in other studies of homosexual men.[2-4] The prevalence for *Giardia lamblia* was lower than generally reported and may be related to a lower prevalence in the San Francisco Bay Area community. In Toronto, Keystone and associates[2] found *Giardia* in 13% of homosexual and 3% of heterosexual men on the basis of a single stool specimen examination; in the San Francisco Bay Area, its occurrence (1.7% on the basis of two specimens in our earlier study[1]) in a smaller percentage of the general population may correlate with its lower prevalence in the homosexual community. The symptoms associated with giardial infection, however, may result in early treatment and thus in lower prevalence of infection in the persons surveyed. We have found this relatively low prevalence of giardiasis generally to exist in our survey of the gay community. The rarity of *Dientamoeba fragilis* infections in the homosexual population may be related to the fact that this parasite seems not to be transmitted by the oral-anal route but may involve concurrent *Enterobius* infection.[5] *Enterobius* is a parasite seen more commonly in children and their parents than in adults having no direct contact with children.

It is difficult to estimate the degree to which self-selection of symptomatic persons or other factors biases the results obtained in a survey such as this. We have a measure of present symptoms based on the answers to nine questions asked of each participant (adapted from questions used in the Toronto survey[2]) regarding the presence of the following problems: (1) stools softer than usual, (2) bowel movements more frequent than usual, (3) increased bloating, belching or burping, (4) increased passing gas by rectum, (5) nausea, (6) increased unexplained fatigue, (7) loss of appetite or weight loss, (8) foods that are usually enjoyed suddenly causing disagreeable symptoms and (9) recent milk intolerance. The same questions were asked of a large number of persons who had the multiphasic health examination in Oakland. From this group of questionnaires, the responses of 102 persons matched by age, sex and race were compared with those of the 102 health fair volunteers completing the questionnaires, including the questions regarding age and race. The average number of positive responses to the nine questions was 1.59 in the health fair group compared with 0.68 in the multiphasic group. Of the health fair group, however, 44 (42%) responded "no" to all nine questions. Of the 44, 12 (27%) were infected with potential pathogens. No correlation between symptoms and the presence or absence of infection could be detected.

Although some degree of self-selection is suggested by the above comparison, presumably it is less than that seen in most other surveys of intestinal parasitic infections in homosexual men, in which statistics were derived either entirely or in part from persons visiting clinics. Thus, we can conclude that these infections are present in a large percentage of the gay community, at least in the larger cities that have been surveyed. Any physician treating homosexual men must be aware of the likelihood of such infections, even in asymptomatic persons.

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Rattlesnake Bites in Northern California

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In a series of 59 cases of rattlesnake bites at two major northern California hospitals, no deaths occurred, no amputations or fasciotomies were required and only one patient had tissue necrosis requiring a graft.

Because patients are being seen in major medical facilities earlier, envenomation is encountered in earlier stages. Less specific national standards of treatment, therefore, should receive less emphasis than treatment based on the virulence of the snakes in the particular geographic region. Initial doses of antivenin given intravenously should be based on the degree of envenomation, with additional titration done for worsening symptoms.

Rattlesnake bites in northern California are not infrequent. The number of resulting deaths in the region appears to be relatively low.[1] Often bites occur to curiosity seekers or hobbyists who play with or keep poisonous snakes as pets. Of 40 subspecies of rattlesnakes throughout the country, only *Crotalus viridis oreganus* (Northern Pacific rattlesnake) is found in this area. This species of snake is also found in Washington and Oregon.[2] Because of the wide geographic distribution of this reptile and the locally relatively mild effects of its bite, the following study is being reported. I review the cases of 59 patients bitten by rattlesnakes and treated in two major hospitals in Santa Clara County (California) between the years 1964 and 1981. All but two bites were from the local species of rattlesnake. An attempt is being made to standardize the treatment of snakebites.

Signs and Symptoms of Snakebite

The classical symptoms of rattlesnake bites, namely pain and swelling, progressively worsen if antivenin is not given. In addition, patients uniformly appear agitated and perioral paresthesias or numbness develops with envenomation (Table 1). In very young children, fang marks are an important sign in determining the cause of pain and swelling. The pain is often severe and initially is localized to the bite site. Pain worsens as the tissue continues to swell acutely, not only in the bite area but also frequently in the regional lymph node bearing areas (axilla or groin). Lymphadenopathy is not uniformly seen in association with this pain. Ecchymosis of local adipose tissue due to microvascular and macrovascular tissue destruction occurs immediately and worsens locally, ultimately causing blistering of the bite area. This takes from 12 to 24 hours to develop.

Due to the fact that our geographic area (Santa Clara County) has a single species of rattlesnake, the problem of identification is relatively simple. One must be aware, however, that hobbyists often import snakes from other areas. This was the case in two patients treated in this series, both of whom had been bitten by a western diamondback rattlesnake, *Crotalus atrox*.

Evaluation of Treatment

Evaluation and treatment are done simultaneously because the status of a patient who is bitten is constantly changing and the treatment must be modified accordingly. The basic evaluation should follow a grading system (Table 2) with regard to the worsening of symptoms. The earlier a patient is seen following a bite, the lower the grade. The grading system is based on the symptom complex common to most rattlesnake bites, namely, swelling, pain and systemic responses. Other factors may be introduced that may alter the treatment and even necessitate a more radical approach, such as surgical excision or fasciotomy.

Common to most cases of bites in which envenomation ensues in our geographic area are immediate swelling, local pain and perioral paresthesias. Muscular fasciculations are rare and neurologic symptoms such as ptosis and paralysis are absent. Patients with bites untreated for 12 hours or more often have significant blistering and local ecchymosis, regardless of subsequent treatment. Because progression of swelling is often difficult to assess, standard measurements of

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extremity circumferences are recommended and on admission these points of reference should be drawn directly on the patient and a running chart kept (Table 3). An evaluation form already exists.[5]

Measurements should be obtained at 15-minute intervals until the effects of antivenin have noticeably reduced the swelling, then at 30-minute intervals for two hours to establish that no progressive worsening is occurring. Following this, measurements should be done once an hour for two hours and then every four hours. If swelling recurs after an initial quiescence, therapy should be reinstituted.

TABLE 1.—*Symptoms and Signs Common to Envenomation by* Crotalus viridis oreganus

Progressive swelling at point of bite
Local pain in area of bite
Perioral paresthesias or numbness
Regional lymph node pain without nodal hypertrophy
Agitation

TABLE 2.—*Definition of Gradation for* Crotalus viridis oreganus *Rattlesnake Bites**

Grade 0
Evidence of snakebite, fang marks
Swelling from site of bite less than 3 cm in 12 hours
No perioral paresthesias
Minimal local pain
Grade 1
Evidence of snakebite, fang marks
Swelling from 3 cm to 15 cm within 12 hours
Severe pain
Perioral paresthesias or numbness
Patient agitation
Grade 2
Evidence of snakebite, fang marks
Progressive swelling of 15 cm to 30 cm within 12 hours
Perioral paresthesias or numbness
Severe pain
Systemic symptoms of nausea, giddiness
Grade 3
Evidence of snakebite, fang marks
Progressive swelling of more than 30 cm in 12 hours
Severe pain
Perioral paresthesias or numbness
Systemic symptoms plus general petechiae and ecchymosis
Grade 4
Evidence of snakebite, fang marks
Swelling of more than 30 cm in 12 hours and/or
Systemic symptoms
Blood-tinged secretions
Renal failure
Shock
Coma
Severe pain

*Modified from McCollough and Gennaro.[4]

TABLE 3.—*Measuring Rattlesnake Bite*

Upper Extremity
Level 1—wrist
Level 2— 6 cm above os pisiforme
Level 3—12 cm below olecranon process
Level 4— 6 cm above olecranon process
Level 5—12 cm above olecranon process
Lower Extremity
Level 1—12 cm above apex of patella
Level 2—12 cm below tibial tubercle
Level 3— 6 cm above medial malleolus

Initial Treatment

The initial treatment requires admission to hospital of all patients who have had rattlesnake bites because an occasional delayed response to envenomation is noted. Intravenous infusion of balanced salt solution is essential and if an upper extremity is involved, the infusion should be in the uninvolved extremity.

A constriction band should be loosely applied well above the area of the bite. Care should be taken not to occlude arterial or venous flow but only lymphatic. This is assured if one or two fingers can comfortably slip beneath the compression band. In my experience, the most common error made by both patients in the field and by hospital personnel is to improperly apply a tourniquet; it is also frequently dangerous. The tourniquet should be moved as swelling progresses to it, using a "leapfrog" technique, until the initial vials of antivenin have been given. It may then be removed.

Tetanus immunization is considered accepted procedure, although *Clostridium* organisms from a reptile's oral cavity are not deemed dangerous.[6] Pain and anxiety changes are common and, in an effort to make a patient comfortable, morphine sulfate and diazepam may be given intravenously. An agitated patient tends to move about extensively, which further propels the venom from its depot through the lymphatic vessels.

Immobilization of the affected extremity is as essential in the hospital care plan as in the field because muscle movement is responsible for lymphatic venom propulsion. Cooling the local area of bite is a controversial procedure. A proponent of this method suggests that it inactivates the venom.[7] There is, however, a question as to further vascular compromise of an already ischemic extremity due to vasoconstriction. Extremity and digit loss have been attributed to its use.[8,9] In our hospital we have leaned away from cooling.

Peripheral noninvasive arterial pulse sensors or serial thermography may be used whenever there is a question of viability of tissue and, in addition, compartment pressure measurements to determine the need for surgical intervention. Intracompartmental pressures above 30 mm of mercury are considered an indication for fasciotomy.[8,10]

Antivenin

Polyvalent crotaline antivenin is now the key therapy for envenomation. Administration of the antivenin is fraught with complications and the insert instructions of the manufacturer (Wyeth Laboratories, Philadelphia, Penn) should be explicitly followed. Not all patients require this medication; eight (14%) of the rattlesnake-bite patients in this series did not have symptoms of envenomation. Russell indicates the number may be as high as 22%.[5]

On admission to an emergency facility, skin sensitization testing should be done first. The antivenin is

given in an intravenous saline drip based on the degree of envenomation (Table 4).

An attempt should be made to administer the maximum dose needed initially because apparently repeated administration separated by time intervals increases the chance of significant horse serum allergic reactions and the occurrence of serum sickness. The antivenin may be titrated to inhibit progressive swelling and also to terminate the perioral paresthesias. It will not immediately reverse the swelling that has already occurred. The initial amount of antivenin given is governed by the volume of venom injected and venom toxicity. This in turn is determined by the snake subspecies and size.

Antibiotics are not generally included in the treatment routine. They do have a role, however, if the snake bite is converted to a human bite when someone sucks on the wound to evacuate venom. In at least two patients in this series such an infection developed. Antibiotics are also of value whenever there is significant vascular compromise. Cultures of specimens from the oral cavity of both wild and pet snakes yield a plethora of Gram-negative bacteria,[6] but it has been hypothesized that these bacteria are heat sensitive and do not survive in warm-blooded mammals.[11] Treatment should therefore be for skin contaminants.

The use of steroids in the treatment of snake bites has been shown to reduce symptoms related to serum sickness; they therefore have a restricted usefulness. Patients with recurrent bites, having once been treated with antivenin, usually have a positive skin test. Desensitization, while a prolonged process, is usually indicated. Steroid administration in this situation is of value.

TABLE 4.—*Recommended Initial Antivenin Dose Grade for* Crotalus viridis oreganus *Envenomation*

Grade	*Vials of Antivenin*	*Grade*	*Vials of Antivenin*
0	0	3	12
1	2	4	..
2	3		

Finally, surgical excision for snakebites has an extremely limited role. Huang and co-workers[12] have reported series in which 50 of 52 patients were successfully treated by excision therapy without the need for antivenin. This procedure is useful in cases of repeat bites, or in field treatment when a patient is more than six hours from an emergency facility and a knowledgeable and medically trained person is present. Incision and aspiration or suction of a bite area has been shown to be effective if done within the first 15 minutes. It is generally not considered a hospital procedure because most patients arrive at hospital more than 15 minutes after a bite (Table 5). The technical aspects include a longitudinal incision through the fang marks in a length equal to the separation of the fang marks and to a depth of 0.5 cm.

Routine laboratory evaluation includes a complete blood count, urine analysis, prothrombin time, partial thromboplastin time and platelet count. Depending on the severity of the bite and the regional difference in the snake venom potency, results of blood typing and crossmatch, electrocardiogram, and measurements of fibrinogen, blood urea nitrogen and serum creatinine levels are helpful. There frequently is an immediate drop in the prothrombin time and platelet count and an elevation of the leukocyte count, the first two of which usually return to normal within 36 hours. The creatine phosphokinase level was measured in three patients and rises were noted within 24 hours, which is probably due to tissue damage at the site of the bite. However, fractionation of this enzyme has not indicated that myocardial damage also occurs (no early venom cardiotoxic effect).

The patients in this retrospective review ranged in age from 4 to 87 years. There were no deaths. As in other geographic areas, rattlesnake bites are most prevalent during the spring and summer months. Eight (14%) of the patients were not envenomated. Most of the patients were considered to have grade 1 and grade 2 bites and were treated accordingly. Interestingly, there were no grade 4 bites in the series. Only one patient sus-

TABLE 5.—*Distribution of Rattlesnake Bites by Grade and Time Delay to Emergency Room From Review of 59 Cases**

Time to Emergency Room (minutes)	*Grade of Envenomation*				
	Grade 0	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
< 15		2	2	1	
< 30	1	2	5	1	
		1	1		
< 60		1	1		
	2	2	4	2	
	1	2	3	1	
	1		3	1	
			3		
<120	1	1	1	2	
		1			
>120			1		
			1		

*Grade and time delay were not recorded in five cases.

TABLE 6.—*Bite Location in Patients Seen at Two Area Hospitals*

Location	*Hospital 1*	*Hospital 2*	*Totals*
Trunk	0	0	0
Extremity	28	31	59
Hand or arm	2	3	5
Fingers	23	26	49
Foot	3	1	4
Toes	..	1	1

TABLE 7.—*Total Antivenin Administration to Patients by Grade of Bite*

Grade	*Number of Patients*	*Antivenin Vials*	*Vials Antivenin per Patient*
0	8 13.6%	3	0.375 (0- 2)
1	20 33.9%	40	2.0 (0- 3)
2	28 47.5%	77	2.75 (1- 6)
3	3 5.0%	36	12 (8-14)
4	0	0	0

tained a repeat bite. Two patients arrived in the emergency room more than two hours after the bite and both of these had grade 2 bites (Table 5). All bites were on the extremities; in 54 out of the 59 cases, they were on the upper extremities (Table 6) and, as expected, the fingers were the most frequently bitten.

Allergies to the antivenin developed in at least two patients during administration requiring the use of diphenhydramine hydrochloride (Benadryl) and epinephrine as treatment. Serum sickness was a late complication and was responsible for four readmissions to hospital. Our patient population tended to be unreliable regarding follow-up visits. There was only one patient documented to have tissue necrosis significant enough to require grafting. None required amputation or fasciotomy.

The average number of units of antivenin given to grade 1 patients was 2, for grade 2 it was 2.75 and for grade 3 it was 12. Apparently *C viridus oreganus* is a less venomous species of snake than snakes encountered in other parts of the country (Table 7). Also, early treatment due to rapid transport to the hospital probably prevents worsening of the symptoms and causes early arresting of the poisonous process short of the stage to which it would normally progress. This arresting of the process in fact may be helped by the large jump of antivenin units given to patients in the grade 3 status. Our recommendation for the dose of antivenin to be given at each grade is based on this idea (Table 4). The amount of antivenin used was proportionate to the severity of the bite. Certainly additional antivenin should be given if worsening continues.

An algorithm for treatment of rattlesnake bites is shown in Figure 1. It is limited to those snakebites that follow the sequential grade progression. Snakes such as *Crotalus scutulatus* (Mojave rattlesnake) have a more neurotoxic venom and are significantly more dangerous, causing fewer progressive symptoms. Treatment of those bites has been discussed in detail by Russell.[5,11,13]

With deep bites or extremity ischemia (or both), compartment pressure measurements are necessary to establish the need for a fasciotomy, 30 mm of mercury appearing to be the critical level.[8,10]

Conclusion

The advent of rapid patient transport to major medical facilities has contributed to the need for reevaluation and adjustment of treatment plans because we now see envenomation in earlier stages. Treatment should be based on the virulence of local reptiles and not on less specific recommendations based on national studies.[3] Emergency room physicians are called on to institute and often control the treatment of rattlesnake bites. Whereas there are a few university centers around

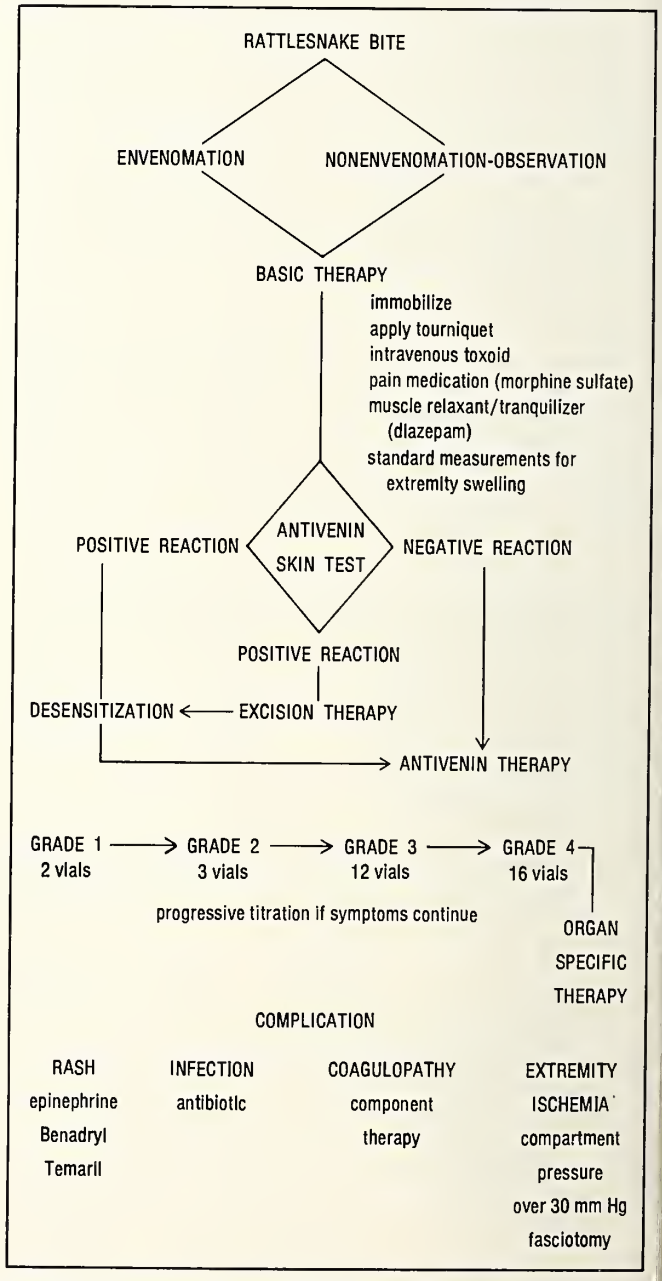

Figure 1.—Schema of treatment of rattlesnake bites that follow the sequential grade progression.

the country that provide specialty treatment, most snakebite patients probably do not end up there for care.

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Articles to Read in Other Journals

Fetomaternal Transfusion Following Trauma

Bickers RG, Wennberg RP

Obstetrics & Gynecology
61:258-259, Feb 1983

DISCIPLINES: Obstetrics, Gynecology, Neonatology, General Practice, Emergency Room Medicine

READABILITY: Very good

Blunt trauma to the abdomen of a pregnant woman, as in automobile accidents, can result in placental disruption and fetomaternal transfusion, threatening the life of the fetus. The authors recommend that Kleihauer-Betke blood smears should be done on pregnant women who have suffered abdominal trauma.

—E. R. W. FOX, MD
Coeur d'Alene, Idaho

Medical Progress

Psoriasis Therapy: A Current Perspective

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Psoriasis is a common papulosquamous skin disease which frequently presents a therapeutic challenge to physicians. Topical therapy with steroids, coal tars and anthralin are effective when used properly for many patients. More severely affected patients may require phototherapy using coal tars and anthralin plus ultraviolet radiation. Systemic methotrexate administration is indicated for some patients with severe skin and arthropathic psoriasis. Treatment using psoralen and long-wavelength ultraviolet phototherapy has recently been approved and is effective in many patients, but long-term safety remains a question. Synthetic retinoids are experimental drugs currently being evaluated for severe forms of psoriasis.

Psoriasis is a common dermatosis affecting between 1.5% and 2% of the population of the United States and northwestern Europe. It is a disease with a variable genetic expression. Recent studies into human leukocyte antigens (HLA antigens) have shown an increased incidence of HLA-13 and HLA-17 antigens. An increased incidence of HLA-27 is found in patients with psoriatic arthritis, particularly sacrolitis. More recently, HLA-Cw6 and DRw7 have been linked with psoriasis vulgaris.[1,2]

Clinically, psoriasis vulgaris is characterized by erythematous, scaling plaques which often begin in the extensor aspects of the body. It may be extremely widespread, with occasional total skin involvement. It is frequently distressing to the patient and occasionally life-threatening.

Other sites affected by psoriasis are nails and joints; approximately 5% to 10% of persons with psoriasis have arthritis. Other clinical types include generalized pustular psoriasis, localized pustular psoriasis of palms and soles, and exfoliative or erythrodermic psoriasis.

Histologically, psoriasis is characterized by acanthosis (thickened epidermis) and parakeratosis (nucleated cells in stratum corneum) and has been described as showing benign hyperplasia. The dermal blood vessels are abnormally tortuous and dilated, and lymphocytic infiltration is frequently seen in the dermis and occasionally in the epidermis.

The epidermal proliferation of psoriatic skin has been studied in detail using radioactive tracers and precursors of nucleic acids. Weinstein and Van Scott, using tritiated thymidine, found a turnover time of normal viable epidermis (that is, basal to granular cell layers) of 14 days compared with two days in psoriatic epidermis.[3]

There are numerous explanations for the increased epidermal cell turnover in psoriasis. Some suggest that there is a loss of the normal control mechanism of epidermal cell production leading to epidermal hyperproliferation, impaired maturation and abnormal keratinization. Conversely, others argue that there is a primary failure in keratinization with abnormal epidermal cell division as a secondary event. Alterations in the epidermal cell cycle times have been found by several investigators in psoriasis compared with normal skin. Weinstein and Frost found the epidermal skin cycle to be 37.5 hours in psoriasis and 457 hours in normal epidermis cells.[4]

Another group used a stathmokinetic method with vincristine and found the cell cycle to last for 55 hours.[5] Thus, though these figures vary, they all suggest a shorter duration of cell cycle. There is continued debate on the details of abnormal cell cycle times in psoriasis.

Attention had been given to possible abnormalities of the cyclic nucleotides in psoriatic skin. However, present results are conflicting. Another research area involves epidermal polyamine abnormalities in psoriasis. Polyamines are basic amines that are intricately

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linked with cellular growth. Their biosynthesis is increased in rapidly proliferating tissues and they have been shown to be increased in psoriasis.[6,7] It is possible that some antipsoriatic drugs act via the polyamine pathway.[8] Abnormalities of the arachidonic acid cascade have been reported in psoriatic skin showing elevation of arachidonic acid and hydroxyeicosatetranoic (HETE) acid with relatively normal prostaglandin levels.[9] Hydroxyeicosatetranoic acid is a chemotactic agent that may possibly be one factor responsible for the epidermal microabscesses containing leukocytes seen in psoriatic epidermis.

Treatment

It is not known whether the available antipsoriatic drugs act to slow cell proliferation primarily or to normalize keratinization. Some of the effective therapies appear to act as antiproliferative agents and reduce rates of either epidermal DNA synthesis, mitosis or both. For example, topical corticosteroids, anthralin, methotrexate, topical 5-fluorouracil, psoralens plus long-wave-ultraviolet light inhibit epidermal DNA synthesis or mitotic rate (or both). Retinoids, however, may act primarily to partially correct the abnormal differentiation seen in psoriasis.

In regard to treatment, cases of psoriasis may be divided into the following groups: (1) psoriasis responsive to conventional topical and physical treatments and (2) more resistant and severe psoriasis requiring systemic therapy.

Topical Steroids

Topical steroids are probably the most widely used of all topical treatments for psoriasis, particularly when given on an outpatient basis, because they are relatively easy to apply. The more potent steroids are sometimes effective at clearing psoriasis and may be used in certain situations—for example, visually obvious areas of psoriasis and flexural psoriasis—however, caution is needed in their use.

The ability of topical steroids to produce vasoconstriction and skin pallor has been utilized to rank them in order of antiinflammatory potency.[10] In most patients the more potent steroids are usually required to produce good responses.

There are certain problems that are seen with the more potent topical steroids: skin atrophy, rebound worsening of psoriasis on discontinuing use of the steroids, a tendency to convert "stable" psoriasis to "unstable" (erythrodermic, pustular) psoriasis, significant skin absorption and systemic effect in patients with extensive psoriasis and the possibility of a rosacea-like syndrome after long-term use of potent topical steroids on the face. As for all steroid-responsive dermatoses, the treatment plan should be to use the weakest strength of steroid that is effective to clear the dermatosis.

Coal Tar Preparations

Over the many decades of its use since Goeckerman[11] described the combination of ultraviolet light and coal tar, many investigators have reached various conclusions concerning the usefulness of coal tar. Numerous modifications of this treatment have been proposed without a clear direction emerging concerning improved therapeutics. Some studies indicate that tar is a useful therapeutic agent[12,13] alone and with ultraviolet light.[14,15] Other reports disagree as to the value of different wavelengths that are used in tar therapy[16] and some investigators find that tar is less necessary in treatment than the ultraviolet light.[17] Any direct comparison of these studies, or the individual experiences of practitioners using coal tar in therapy, is rendered difficult by the various protocols used and the inability to characterize coal tar as to chemical composition or biological activity.

Recently, Levine and co-workers[17] reported that crude coal tar application was no more effective than petrolatum when combined with aggressive ultraviolet-B (UVB)—290 to 320 nm wavelength range—therapy for psoriasis. They, therefore, questioned the need to use coal tar in an aggressive UVB regimen.

Frost and associates[18] had previously reported that a purified tar gel was more effective than gel base alone when combined with suberythemogenic doses of UVB. In this study, psoriasis cleared more rapidly on the tar gel-UVB treated side than on the gel-based-UVB treated side. This study suggests that tar contributed a photoadjunctive effect that enhanced that of the suberythemogenic UVB radiation.

Evidence for a direct effect of coal tar was reported using the skin of normal volunteers,[19] resulting in a transient epidermal hyperplasia followed after 40 days by a significant thinning of the epidermis; and by the ability of crude coal tar to directly suppress epidermal DNA synthesis in hairless mice.[20-22] This assay has been recently confirmed as a useful predictive screen for other agents with potential antipsoriatic properties.[23,24]

We have recently (1) studied the effect of erythemogenic or suberythemogenic dosages of UVB in conjunction with crude coal tar or petrolatum alone, (2) studied the effect of suberythemogenic dosages of UVB with a tar extract in oil or the oil base alone and (3) carried out a direct comparison of a tar extract in oil versus oil base without ultraviolet light to determine any direct effect of tar extract in oil on psoriasis.[25]

These same comparisons of the tar phototherapy regimen were also studied using the hairless mouse epidermal DNA synthesis suppression assay in an attempt to further predict the efficacy and clarify the mechanisms of coal tar phototherapy in psoriasis.

In summary, our study showed

- Erythemogenic UVB and 1% crude coal tar concentration was equipotent with erythemogenic UVB and petrolatum.
- Suberythemogenic UVB and 1% crude coal tar concentration or a coal tar extract in oil was more effective than suberythemogenic UVB and petrolatum.

Therefore, coal tars are directly therapeutic and they enhance the effects of suberythemogenic UVB. They do

TABLE 1.—*Two Commonly Available Proprietary Anthralin Preparations*

Name	*Concentrations percent*
Anthraderm Ointment ...	0.1, 0.25, 0.5, 1.0
Drithocreme	0.1, 0.25, 0.5

not increase therapeutic effects of erythemogenic UVB with petrolatum. The long-term safety of erythemogenic UVB without tar compared with suberythemogenic UVB with tar remains to be determined.

Anthralin

Anthralin is trihydroxyanthracene, an aromatic compound with three benzene rings. It has been used topically for psoriasis since the 19th century. It is available commercially in creams and ointments at present (see Table 1).

Previous descriptions of psoriasis treatment with anthralin have focused mainly on the use of concentrations greater than 0.1%. Ingram used concentrations of more than 0.1%[26]; Seville[27] evaluated the application of 0.5% anthralin paste. Seville also reported that concentrations of 0.25% and 0.1% anthralin improved the conditions of patients with psoriasis and that, interestingly, the relapse rate in these patients was worsened by the addition of topical corticosteroids to the anthralin regimen.[28] Recent studies describing the beneficial effects from lower concentrations of anthralin (0.1% to 0.05%),[29] however, also used concomitant baths with coal tar solutions, ultraviolet radiation and 10% salicylic acid in a petrolatum vehicle. These other modalities alone might be expected to have some beneficial effect on psoriasis. For example, it has been shown that the use of erythemogenic UVB and petrolatum will cause substantial improvement in psoriasis.[17]

Recently we carried out a study to investigate the effects of different concentrations of anthralin on DNA synthesis in hairless mouse epidermis and to study the clinical effects of different concentrations of anthralin on patients with psoriasis.[23] The ability of drugs to suppress hairless mouse epidermal DNA synthesis has been shown to be a useful predictor of antipsoriatic effectiveness.[23,24]

The results described in our studies suggested that the biological and clinical effectiveness of anthralin in acetone or in water-in-oil emulsion is restricted to the use of concentrations of 0.1% or more. The mechanisms of anthralin's effect on psoriasis are not precisely known, but it has been shown that anthralin can reduce the mitotic rate of epidermal cells[30] and that anthralin forms molecular complexes with DNA and suppresses epidermal cell DNA synthesis.[23] These effects may lead to reduced epidermal proliferation and clinical improvement of psoriasis.

Interestingly, recent clinical experiments have shown that much higher concentrations (1% and greater) of anthralin applied to psoriatic lesions and washed off after ten minutes causes improvement.[31] This makes outpatient psoriasis treatment with anthralin practical. Caution is needed, however, to avoid skin irritation with this agent.

Systemic Treatment of Psoriasis

Fortunately, systemic treatment is only needed in patients with severe or incapacitating psoriasis. The following are indications for systemic therapy in psoriasis:

- generalized pustular psoriasis
- generalized exfoliative psoriasis
- severe psoriatic arthropathy
- severe uncontrolled psoriasis
- socially incapacitating psoriasis.

Systemic Corticosteroids

Systemic corticosteroids, particularly triamcinolone acetonide, prednisone and adrenocorticotropic hormone, are occasionally used in the treatment of psoriasis. My own preference is to avoid their use unless the patient has been previously treated with a systemic steroid and has become "steroid dependent."

There is evidence that the use of systemic steroids in psoriasis vulgaris may have led to some cases of severe generalized psoriasis. Occasionally, we have to use systemic steroids in the acute disease where other forms of systemic treatment are contraindicated. On attempted withdrawal of a psoriatic patient from systemic steroid treatment, a severe worsening of the psoriasis may occur.

Some physicians use short courses of systemic steroids for the treatment of acute guttate psoriasis. Again, I have observed rebound worsening of psoriasis developing following such treatment.

Systemic Antimitotic Drugs

Psoriasis is a disease in which there is an increase of the mitotic rate and DNA synthesis in the epidermis.[3,4]

It is not surprising, therefore, that systemic antimitotic agents have been used in the control of this disease, but it is to be emphasized that this group of drugs carries a significant number of potential side effects.

Methotrexate

The most widely used of the antimitotic agents in the United States is methotrexate, and it is mainly given by mouth, though it may be given intramuscularly or intravenously.[32] It is important that pretreatment liver biopsy specimens be taken and show no evidence of hepatic fibrosis (a significant potential side effect of methotrexate). In addition, normal blood cell counts, platelets, hepatic function and renal function must be confirmed before treatment.[32] If needed for psoriasis, then methotrexate should, if possible, be reserved for chronic unresponsive psoriasis in patients past the reproductive age. The patient must be willing to have weekly, then monthly, blood specimens taken to ensure absence of side effects.

Some recommend that oral regimens be three doses

per week spaced at 12 hour intervals; this follows the finding that the mean epidermal cell cycle time in psoriasis is 37.5 hours.[3] There has been recent controversy over this cell cycle time, however, and my own preference is to give methotrexate once a week by mouth. If there is significant nausea from oral administration, I then prefer to use the intramuscular route. Usually a test dose of 5 mg to 7.5 mg is given and the patient response is observed over the next five to seven days. Increased dosage is then given until good response is seen. A complete blood count should be done at each visit and biochemical studies carried out regularly. Bone marrow suppression may occur, but other side effects such as renal, bowel and lung toxicity are not expected in dosages used for psoriasis therapy.

Methotrexate is known to interact with several drugs that may displace methotrexate from plasma albumin binding, thereby increasing potential toxicity. These drugs include sulfonamides, salicylates, barbiturates, probenecid, phenylbutazone and colchicine. Overdosage of methotrexate must be treated promptly with leucovorin-citovorum.

The guidelines of methotrexate therapy have recently been reviewed[32] and that review is recommended for further details.

Other Antimitotic Drugs

Other antimitotic drugs used over the years in the treatment of psoriasis include azathioprine, hydroxyurea, cyclophosphamide and azaribine. However, none have been as successful as methotrexate, or they have had serious side effects (for example, the thromboembolism from azaribine). Recently, mycophenolic acid has been used in the systemic treatment of psoriasis, but there is a 30% incidence of diarrhea and other symptomatic gastrointestinal effects, in addition to an increase in viral infections, neutropenia and possibly an increased incidence of internal carcinoma.[33]

Razoxane, an antiproliferative drug that arrests cells in the G2 phase of the cell cycle, has recently been evaluated in England. It appears to have good promise as a potential systemic agent for therapy of psoriasis.[34] However, it does have toxic effects on the bone marrow.

Photochemotherapy of Psoriasis

A significant alternative treatment for recalcitrant and severe psoriasis is psoralen photochemotherapy. This treatment (PUVA) involves the use of the photosensitizing drugs psoralen (P) and long-wavelength (320 to 400 nm) ultraviolet light (UVA). Walter and co-workers described this treatment in 1973 using topical methoxsalen and UVA.[35] In 1974 a group from Boston described the use of oral methoxsalen and UVA in psoriatic patients.[36]

At present, we do not know if such delayed side effects as premature skin aging and skin carcinogenesis from this treatment will occur and we probably will not know for the next 10 to 15 years.

Psoralens have been used for many years in the treatment of vitiligo; and so, the new and unknown quantity of PUVA is really the high intensity UVA light sources that are necessary to produce a good therapeutic response and maintenance control in psoriasis. There is the danger, however, that the treatment will be carcinogenic for the skin in some susceptible patients.[37] The groups of patients most at risk of skin cancer following PUVA seem to be patients with lighter skin who sunburn readily and patients who have received previous x-ray therapy to their skin. Such patients probably should not receive PUVA therapy. Theoretically, we may see premature skin aging from the dermal effects of the UVA.

PUVA should probably only be available at centers that have the facilities to carefully monitor UVA dosing and the patients until results of long-term treatment are available.

Early and usually mild transient side effects are pruritus and phototoxic erythema. Occasionally nausea is a problem. It is possible to combine systemic PUVA with a topical therapy and in some patients enhance the psoriasis clearing. In one study, anthralin was combined with PUVA, with more rapid clearing in the anthralin-PUVA treated patients.[38]

At present, PUVA should probably be reserved for severe or recalcitrant psoriasis resistant to topical therapy. It may help some patients with generalized pustular or exfoliative psoriasis, but great care is needed to avoid worsening of psoriasis in these patients with PUVA therapy.

Synthetic Retinoids

Synthetic retinoids used systemically, such as the aromatic retinoid RO-10-9359, now are under study at several centers in the United States and result in significant improvement in some cases. The dosage has to be monitored closely to control side effects (including cheilitis, itching, fragile skin, thirst, sore mouth, and palm and sole peeling). In approximately 60% to 70% of patients, good responses are achieved and the benefits of treatment outweigh the side effects. An unresolved problem with the systemic synthetic retinoids is abnormalities of serum lipids in some patients. The significance of this finding remains unknown.

We have recently studied the effects of RO-10-9359 in patients with severe psoriasis previously receiving therapy with methotrexate, systemic steroids or PUVA. In 17 of 21 patients, the disease is well controlled after two years of RO-10-9359 therapy alone, in dosages between 0.25 and 1.0 mg per kg of body weight per day. Seven of these patients had psoriatic arthropathy, which lessened in four patients while taking the retinoid. When the drug was discontinued, psoriasis relapsed in an average of eight weeks but rapidly responded when retinoid therapy was begun again.[39]

In Europe combinations of systemic retinoid and anthralin have been used with success.[40] The combination of systemic retinoids with other treatments including UVB and PUVA is proving to be successful in European studies. These experimental drugs hold new promise for a variety of severe skin diseases including

TABLE 2.—*Some Treatments of Psoriasis in Specific Sites*

Type of Psoriasis and Treatment
Palmar, plantar psoriasis Potent topical steroid creams under plastic wrap (or plastic gloves) 5% coal tar in Lassar's paste; anthralin preparations; local UVA and topical and systemic psoralen and local UVA often very effective. Synthetic retinoids.
Mild scalp psoriasis Topical steroid lotions. Tar gels, tar oils or phenol and saline (P and S) liquid applied at night and shampooed with tar in the morning. Steroid lotions applied twice a day. Tar shampoos daily.
Severe scalp psoriasis 5% coal tar and 5% salicylic acid ointment or tar gel or tar oils overnight; mineral oil to scalp in morning to "loosen ointment," then shampoo with tar, alternative: 0.4% anthralin pomade at night. Steroid lotions twice a day.
Usage of Tar Shampoos in Psoriasis of the Scalp The hair and scalp should be wet, the tar shampoo rubbed well into the scalp; the scalp is then wrapped with a towel for 15 minutes and then the shampoo washed out with running water.
Nail Psoriasis Triamcinolone injection (2.5 to 10 mg per ml) intradermally, administered carefully into proximal nail fold occasionally improves nail disease. Severely hyperkeratotic nails may be removed using 40% urea paste overnight.

psoriasis, but are not approved by the Food and Drug Administration for psoriasis. Oral 13-*cis*-retinoic acid has been approved for treatment of severe pustulocystic acne.

We have recently studied the effectiveness of combinations of 13-*cis*-retinoic acid plus anthralin or plus UVB phototherapy. Of ten patients, nine improved significantly, but it remains to be seen if there is a role for this drug in psoriasis. It is not approved for this disease and any studies are experimental.

Psoriasis Outpatient Treatment Centers

There is a need for specialized centers with physician and nursing staff experienced in psoriasis therapy. Such centers ideally combine all the therapeutic modalities because some patients respond at different times to these alternative therapies. Outpatient treatment centers are able to offer modified Goeckerman, modified anthralin and PUVA treatments. Some patients often are able to continue to work and are able to have their treatment without disrupting their daily lives, avoiding lengthy and expensive hospital stays. Some patients with severe recalcitrant psoriasis, however, still often require a full day's therapy at a day-care center or admission to hospital.

Summary

Psoriasis is a chronic and relapsing disease, hence constant patient reassurance is important. No permanent cure is available, but it is possible to achieve complete clearance for a time in many patients (Table 2). Complications such as generalized erythroderma and pustulation are best treated in a hospital. The use of cytotoxic or phototoxic (PUVA) therapy for the severe, intractable or potentially lethal forms of psoriasis requires careful supervision, for obvious reasons.

Systemic use of steroids in the past frequently led to a severe relapse upon withdrawal. This therapy is now rarely indicated. Topical steroid treatment under plastic wrap occlusion or with very potent topical steroids without occlusion is very effective, but remission times are often relatively short. Occasionally, severe relapse on withdrawal makes the disease "unstable."

Newer systemic agents such as synthetic retinoids are becoming available for the therapy of psoriasis, resistant to either topical therapy or ultraviolet phototherapy.

Hopes for the Future

A major hope would be for a primary defect in psoriasis to be discovered. Is this defect epidermal or dermal? Is it a result of abnormal dermal vasculature? Is it a result of an abnormal biochemical pathway in the epidermis? If these basic questions could be answered, then further advances in therapy may be possible.

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Articles to Read in Other Journals

Correlation of Decrease in Perinatal Mortality and Increase in Cesarean Section Rates

O'Driscoll K, Foley M

Obstetrics & Gynecology
61:1-5, Jan 1983

DISCIPLINES: Obstetrics, Gynecology, General Practice, Pediatrics

READABILITY: Very good

In the United States the cesarean section rate has risen to more than 15 percent while perinatal mortality has had a significant decrease. The authors contend that this is a coincidental rather than a causal relationship, because neonatal mortality rates in the British Isles have shown a similar decrease, while cesarean section rates continue to be under 5 percent.

—E. R. W. FOX, MD
Coeur d'Alene, Idaho

Specialty Conference

Hypertension Symposium: Newer Topics on Normal and Abnormal Blood Pressure Regulatory Mechanisms

Moderator
MICHAEL L. TUCK, MD

Participants
MICHAEL S. GOLUB, MD; PETER EGGENA, PhD; JAMES R. SOWERS, MD, *and* MORTON MAXWELL, MD

Taken from a Symposium on Hypertension, Department of Medicine, UCLA School of Medicine, San Fernando Valley Program at the Veterans Administration Medical Center, Sepulveda, California, as part of Medical Grand Rounds, Stanley G. Korenman, MD, Director, June 2, 1982.

For years essential hypertension was regarded as a relatively uniform disease having one predominant but uncertain cause. We now recognize that blood pressure is regulated by an interplay of factors that include vascular hemodynamics, pressor and depressor hormones, volume and sodium alterations, neural stimuli and renal dynamics. It is now clear that no single aberration can explain this disorder. Whether a person with essential hypertension has one or multiple pathophysiologic changes is still debated just as vigorously as the concept that patients who have this disorder can be neatly divided into subsets based on differences in certain blood pressure regulatory systems.

This conference focuses on several new and controversial areas in the pathogenesis of essential hypertension. Cellular sodium transport abnormalities have recently been rediscovered in this disorder and add new evidence to the concept that sodium may have an important role in essential hypertension. Other epidemiologic factors have taken on new importance in blood pressure control, and obesity and its attendant metabolic aberrations serve as an excellent example of this problem. The renin-angiotensin system is one of the best characterized blood pressure control systems in essential hypertension. Yet only recently with the ability to block the effect of angiotensin II has the participation of this system in essential hypertension been better defined. The recently discovered complexity of the components of this system (inactive renin, tissue renins) has introduced new thoughts on its role in blood pressure control. The ultimate goal in drug treatment of essential hypertension would be the use of agents that specifically attack a given abnormality. The introduction of the converting enzyme inhibitors and calcium channel blockers may be a step in this direction.

Sodium Transport in Hypertension

MICHAEL TUCK, MD:* A cause-effect relationship between sodium intake and hypertension was one of the earliest considerations in the pathogenesis of this disorder. Numerous epidemiologic studies show a strong correlation of average daily salt intake and the prevalence of hypertension in different geographic areas.[1] It has been more difficult, however, to establish this relationship in societies wherein salt intake is high and examination of blood pressure levels in normal persons with varying salt intakes may not show any differences. It is possible, however, that within populations the level of blood pressure of certain persons or families is more dependent on salt intake. This differing sus-

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ABBREVIATIONS USED IN TEXT

G6PD = glucose-6-phosphate dehydrogenase
K_m = Michaelis-Menten constant

ceptibility to high salt intake may have a genetic basis and may originate in the mechanisms whereby sodium is transported across cell membranes. The concept of salt susceptibility was first championed by Lewis K. Dahl,[2] who developed a strain of rats that responded to high salt intake by having pronounced hypertension develop and another strain in which blood pressure was resistant to high salt intake. Although not yet proved, these findings in experimental hypertension are possibly comparable to human essential hypertension. Another early observation from Tobian[3] was that cardiovascular tissues from patients who have hypertension have a higher sodium content than those from their normotensive counterparts. One explanation for high intracellular sodium in hypertension is that sodium transport pathways may be abnormal in the cells of hypertensive persons.

In 1960 Losse and co-workers first noted high intracellular sodium concentration in erythrocytes of essential hypertensive patients and suggested this was due to abnormal sodium transport in this cell.[4] Most cation transport studies in human hypertension have been on erythrocytes, polymorphonuclear leukocytes or lymphocytes because of their accessibility. In human erythrocytes the extrusion of sodium is mediated mainly through the adenosine triphosphate-dependent sodium-potassium pump, which is inhibited by cardiac glycosides such as ouabain (Figure 1). There exist in this cell, however, at least two other sodium transport systems that are not inhibited by ouabain (ouabain-insensitive pathways). These are the Na^+, K^+ cotransport system,[5] which catalyzes the coupled transmembrane efflux or influx of Na^+ and K^+ in the same direction, and the Na^+, Li^+ exchange or countertransport system, which represents a one-to-one exchange of Na^+ for Na^+ or Li^+ for Na^+ across the plasma membrane (Figure 1).[6] Detection of abnormalities in these transport systems in erythrocytes from patients who have essential hypertension is the main consideration in this review.

Garay and Meyer first noted abnormalities in the Na^+, K^+ cotransport system in erythrocytes from patients with essential hypertension.[7,8] This system is identified by examining Na^+ and K^+ efflux rates in the presence of ouabain and furosemide in erythrocytes preloaded with Na^+ and depleted of K^+.[7-9] Furosemide is the specific inhibitor of cotransport activity. Maximal outward furosemide-sensitive cotransport of Na^+ and K^+ is significantly reduced in erythrocytes from about 70% of patients with essential hypertension (Figure 2).[9] Moreover, a familial pattern of defective erythrocyte cotransport is seen in a substantial number of normotensive offspring from families with hypertension. Thus, it is possible that there is a genetic transmission of this trait that would offer the potential of this assay to detect hypertension-prone offspring from families with a high prevalence of hypertension. Interestingly, patients with secondary hypertension (mostly renovascular hypertension) showed normal cotransport if they had no family history of hypertension, whereas those with a family history had reduced cotransport. The cotransport abnormality appears to occur independently of the level of blood pressure, duration of hypertension and sex and age of patients.[9] Garay and associates have proposed that decreased Na^+ cotransport in hypertension is due to a reduced affinity of

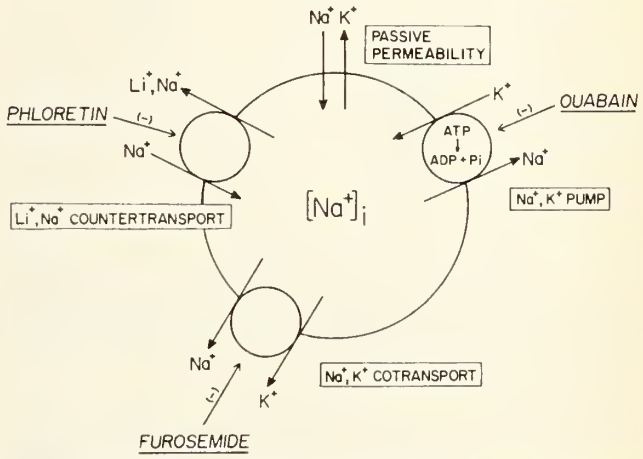

Figure 1.—Human erythrocyte sodium (Na^+) transport systems that have been examined in hypertensive disorders. K^+ = potassium, Li^+ = lithium, ADP = adenosine diphosphate, ATP = adenosine triphosphate, Pi = inorganic phosphate.

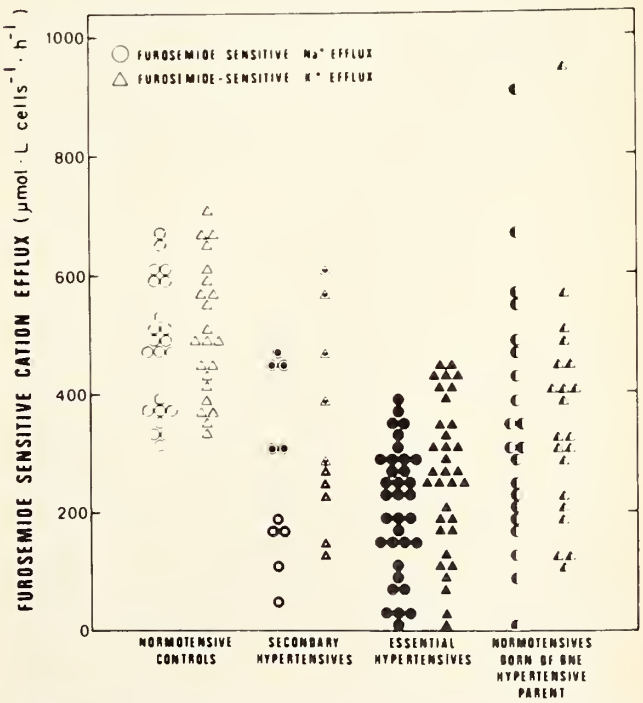

Figure 2.—Scatter diagram of the maximal rate of outward furosemide-sensitive sodium (Na^+)-potassium (K^+) cotransport in hypertensive disorders (from Dagher and Garay[9]).

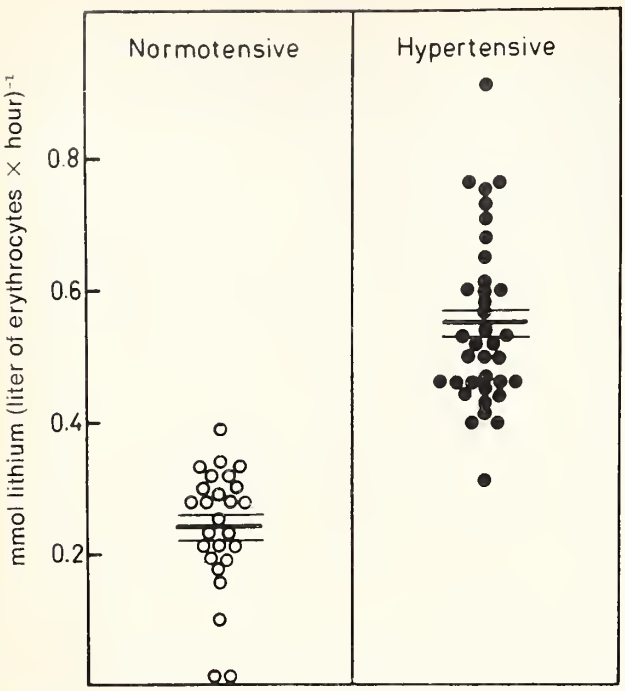

Figure 3.—Maximal rate of sodium-stimulated lithium efflux in erythrocytes of normotensive subjects and patients who have essential hypertension (from Canessa et al[18]).

internal Na^+ for the binding sites on the cotransport pathway.[10] Thus, in erythrocytes from essential hypertensive patients half-maximal cotransport stimulation occurs at an intracellular Na^+ concentration of about 20 mmol per liter of cells compared with 10 to 15 mmol in normotensive cells. At present it may be premature to comment on the possibility of the cotransport assay as a genetic marker of this disorder. Likewise, the pathogenetic significance of reduced cotransport remains speculative. One could postulate that in vascular smooth muscle cells a defective outward movement of Na^+ would lead to an abnormally high intracellular Na^+ concentration leading to excessive excitability of these cells.

Confirmation of reduced erythrocyte Na^+, K^+ cotransport in the essential hypertensive population has not been uniform. One report[11] noted reduced inward cotransport of rubidium, a substitute for potassium, in about 75% of patients who have essential hypertension, whereas others[12] detected this abnormality in less than half their patients. Normotensive offspring of hypertensive parents had intermediate cotransport values, but a great overlap was noted in individual values between normotensive and hypertensive groups. A study of erythrocyte cotransport from Cape Town, South Africa, included both black and white persons with essential hypertension.[13] This group noted that though mean cotransport values were lower in hypertensive persons, the overlap was too large to make it a useful genetic marker in hypertension. They also could find no significant difference in cotransport function between black and white persons who had hypertension. These findings contrast with another report from the Ivory Coast of Africa where the incidence of hypertension is extremely high and levels of cotransport were uniformly low to absent in erythrocytes from hypertensive subjects.[14] Other studies have not been able to detect any abnormality in cotransport in patients with essential hypertension.[15-17] It is doubtful, however, that the latter reports using small study groups really disprove the original observation of abnormal outward Na^+, K^+ cotransport in some patients with essential hypertension, especially since the methods of measuring cotransport varied widely in these reports.

A second abnormality was reported by Canessa and co-workers[18] who found increased Na^+, Li^+ countertransport in erythrocytes from essential hypertensive subjects. This pathway is a one-to-one Na^+ exchange across the erythrocyte membrane and results in no net transport of ions. To measure countertransport, erythrocytes are loaded with lithium, which can substitute for internal sodium and has a greater affinity for the transport system, ensuring maximal rates of efflux. The difference in rate of loss of Li^+ from cells in the presence and absence of external Na^+ defines the Na^+, Li^+ countertransport pathway. Mean countertransport values were about twice as high in erythrocytes from persons who had essential hypertension with little overlap of values from those with normal blood pressure (Figure 3). Similar to the cotransport system, countertransport was also abnormally high in first-degree relatives of patients with essential hypertension. Previous studies on Li^+ transport in bipolar mood disorders also described a genetic transmission of the countertransport pathway.[19]

Several other studies have now confirmed that hypertensive subjects have increased erythrocyte Na^+, Li^+ countertransport.[12,20-23] Some of these reports found larger individual overlap and one study noted that only those patients with at least one hypertensive first-degree relative had elevated countertransport. Some have concluded that the assay is not a consistent marker for essential hypertension.[20] In a study of black school children a significant positive relationship between erythrocyte countertransport and systolic blood pressure was found,[21] thereby supporting a relationship between cellular sodium fluxes and blood pressure in this younger population. Normotensive offspring of hypertensive parents appear to have intermediate increases in erythrocyte countertransport. Woods and colleagues[22] examined the Na^+, Li^+ countertransport in 18 teenage sons of parents with essential hypertension and 21 sons of normotensive parents and noted that the rate was significantly increased in black and white male offspring of hypertensive parents. There may also be unexplained geographic differences in maximal rates of Na^+, Li^+ countertransport as there have been differences in absolute values reported from different parts of the world.[24] Only ongoing studies will further elucidate the genetic factors in countertransport function by examining large numbers of well-characterized families with essential hypertension. Two recent reports[17,25] using different assay techniques to measure Na^+, Li^+

exchange in erythrocytes could find little difference between hypertensive and normotensive persons.

Several questions about the importance of abnormal ouabain-insensitive Na^+ transport pathways in essential hypertension remain to be answered. Does a hypertensive person who has abnormal erythrocyte sodium transport also have blood pressure sensitivity to a high sodium intake? This observation would offer the theoretic potential of using the erythrocyte assays as indicators of persons with blood pressure susceptibility to high salt diets. The exact relationship between a reduced erythrocyte Na^+, K^+ cotransport system and a high Li^+, Na^+ countertransport system in a hypertensive person also needs further explanation. Most investigators feel that they are two different transport systems, but it is also feasible that they may be two operationally different modes of the same transport system.[24] Uncertainty also exists as to whether genes determining transport activity of these two systems are identical or different. Studies are now in progress measuring both transport systems in the same hypertensive persons and their offspring. Preliminary findings indicate that there may be various subsets of erythrocyte Na^+ transport abnormalities in the essential hypertensive population such as high countertransport-low cotransport, high countertransport-normal cotransport and perhaps other combinations.[26] Finally, the question remains whether the transport abnormalities in erythrocytes from persons with essential hypertension reflect the sodium and potassium ion transport capacity of more relevant target tissues such as vascular smooth muscle in essential hypertension. One postulate is that similar defects in vascular smooth muscle would result in high intracellular Na^+ concentrations that could influence Ca^{++} concentrations, leading to activation of the contractile process and increased vascular resistance.[27]

Studies of the ouabain-sensitive sodium-potassium pump, the major system for cation transport in cells, show a spectrum of findings in hypertensive disorders. Many animal models of hypertension, especially those with volume-dependent hypertension, show reduced target tissue sodium-potassium pump activity whereas measurements of pump activity in tissues from persons with essential hypertension show varying results. There are several methods for characterizing the ouabain-sensitive sodium-potassium pump, including membrane sodium-potassium-adenosine triphosphatase activity, ^{86}Rb uptake, ouabain binding and measurement of unlabeled cation fluxes in the presence and absence of ouabain. These methods differ widely in techniques and tissue preparations.

Ouabain-sensitive Na^+ transport (sodium-potassium pump) has been found to be reduced, normal or increased in cells from patients with essential hypertension. Edmondson and co-workers[28] reported reduced ouabain-sensitive sodium transport in leukocytes of patients who have essential hypertension. Other reports describe reduced ouabain-sensitive Na^+ efflux rate constants in black Africans with essential hypertension[29] and in white patients.[30] Further investigations of racial differences in cation transport show that the ouabain-sensitive uptake of rubidium was lower in erythrocytes from black than from white normotensive persons.[31] Alterations in plasma volume and salt intake may also influence the activity of the sodium-potassium pump. Poston and colleagues[32] reported decreased ouabain-sensitive Na^+ efflux rate constants in leukocytes from untreated persons with essential hypertension and further observed that diuretic therapy reversed this abnormality. Salt intake in hypertensive persons may also influence cellular Na^+ transport, as one report indicated that a high salt intake in hypertensive persons reduced erythrocyte ^{22}Na efflux rate.[33]

Normal sodium-potassium pump activity in cells from patients who have essential hypertension and their normotensive offspring has also been observed.[12,34,35] One such study[34] could find no significant difference between erythrocytes of normotensive and essential hypertensive persons in sodium-potassium-adenosine triphosphatase activity and its Michaelis-Menten constant (K_m) value for adenosine triphosphate or in active ouabain-sensitive cation fluxes. They concluded that determination of these values in erythrocytes is not useful in the detection or diagnosis of essential hypertension. Ouabain-binding studies also show[35] no difference in the number of erythrocyte-binding sites between hypertensive and normotensive persons, suggesting normal sodium-potassium pump units in patients who have essential hypertension.

Actual increases in sodium-potassium pump activity have also been reported in cells from essential hypertensive patients. Woods and co-workers[31] showed that there was a greater activity of the sodium-potassium pump in fresh erythrocytes and Wambach and associates[36] reported greater adenosine triphosphatase activity in erythrocyte ghosts from patients with essential hypertension. Cation flux studies also show that outward ouabain-sensitive sodium efflux is increased in patients who have essential hypertension and certain of their normotensive offspring.[37] The increased sodium-potassium pump activity in essential hypertension has been proposed to be a compensatory response to abnormalities in the ouabain-insensitive transport systems described in the cells of these patients.

Considerable evidence supports the existence of a circulating humoral agent other than aldosterone that controls urinary sodium excretion by inhibiting sodium transport. This proposed natriuretic hormone probably acts on the sodium-potassium pump as it has been shown to inhibit renal sodium-potassium-adenosine triphosphatase activity.[38] Sodium-potassium-pump inhibition by natriuretic hormone in renal tissue may extend to other tissues such as vascular smooth muscle wherein the potential effects of sodium transport inhibition would lead to intracellular sodium accumulation. Thus, hypertensive persons, who are known to have an exaggerated natriuresis to sodium loading, may have exaggerated responses of a natriuretic-like hormone substance in response to salt loading, leading to a reduction of blood volume through enhanced renal sodium

excretion, while increasing inhibition of vascular smooth muscle pump activity. In volume-expanded animal models of hypertension there is a consistent reduction in pump activity as reflected by reduced arterial tissue rubidium uptake and cardiac microsomal adenosine triphosphatase activity that may be due to a circulating sodium transport inhibitor.[39,40] These observations have been extended by MacGregor and co-workers[41,42] to human essential hypertension in which they examined the ability of the plasma from hypertensive subjects to stimulate guinea pig renal glucose-6-phosphate dehydrogenase (G6PD), a marker of inhibition of the sodium-potassium pump. There was a significant increase in the ability of the plasma from patients with essential hypertension to stimulate G6PD compared with plasma from normotensive controls. These results suggest that patients with essential hypertension have enhanced levels of a circulating inhibitor of sodium-potassium pump activity. In cross-incubation experiments by adding leukocytes from normotensive persons to plasma from hypertensive patients there is impairment of sodium transport and this correlates inversely with the level of plasma renin in the hypertensive persons.[43] It was suggested that the degree of volume expansion and renin reduction related to the severity of pump suppression in these patients.

The idea of a putative circulating inhibitor of sodium transport in patients with essential hypertension is exciting and might explain some of the previously described sodium transport abnormalities in this disorder. The leading candidate for this inhibitory function seems to be a natriuretic hormone or a closely related compound. Isolation, purification and characterization of a sodium-potassium-pump inhibitor remains a problem despite several years of work in this area. Many experts agree it may be a peptide because enzymes that destroy peptides block its action. Another path of exploration has offered evidence that it may be a cardiac glycoside-like substance. Gruber and colleagues[44,45] showed in plasma from salt-loaded dogs a factor that cross-reacts with antidigoxin antibodies. They termed this digoxin-like substance "endoxin" and have identified it in animals that have hypertension.

Conceivably, from the abnormalities reported in membrane sodium transport and the proposed humoral control of this function, a stronger relationship between salt intake and hypertension may be established. Although certain observations continue to conflict, they point towards major research efforts in this area. Certainly the assays for membrane transport need to be improved as so little is known about the cotransport and countertransport systems and their contribution to cellular cation balance. At present these assays are difficult and complicated, making their clinical use somewhat limited. Any further progress in the role of natriuretic hormone in hypertension will depend partially on further isolation and identification of this substance. The relationship between these membrane and humoral defects in hypertension and the results of epidemiologic and therapeutic studies of salt intake in hypertension are also beginning to be examined.

New Probes of the Renin-Angiotensin System

MICHAEL GOLUB, MD:* In 1898 Tigerstedt and Bergman noted that a kidney extract raised blood pressure in recipient rabbits.[46] They named the active material renin. Although this discovery did not excite the scientific world,[47] it provided the background for the important experiments of Harry Goldblatt in the 1930s. When Goldblatt found that renal ischemia could lead to hypertension in experimental animals,[48] the possibility that renin might underlie hypertension in humans became an important hypothesis.

The subsequent discovery of the renin-angiotensin-aldosterone cascade has led to a physiologic understanding of how this system can help raise blood pressure. Renin is a proteolytic enzyme that cleaves a decapeptide, angiotensin I, from a large substrate molecule manufactured in the liver. Angiotensin I is rapidly converted in the lung, kidney and plasma to the octapeptide, angiotensin II. The enzyme responsible for this important conversion reaction is called angiotensin-converting enzyme. Angiotensin II is a potent pressor substance but has the additional property of stimulating the adrenal gland to produce the sodium-retaining mineralocorticoid, aldosterone. Thus, any factor that stimulates renin release from the kidney would be expected to increase circulating levels of angiotensin II and aldosterone, both of which are potent hypertensive agents.

Clinical medicine has confirmed that in many patients who have disease of the renal arteries, renin-secreting tumors and other renal disorders (trauma, infarct, acute ureteral obstruction) hypertension can develop because of increased activity of the renin-angiotensin system. If renin activity can be lowered or angiotensin II can be antagonized in these patients, blood pressure will fall.

The role, however, of the renin-angiotensin system in maintaining elevated blood pressure in essential hypertension has continued to produce controversy. Brunner and Gavras have reviewed the physiologic role of the renin-angiotensin system in humans[49] and have concluded that this system developed to defend the organism from severe volume and sodium deficits. Thus, in normal persons living in high-sodium-intake societies the system should be relatively quiescent, but this may not be the case in hypertensive persons.

The findings of recent research have supported the concept that the renin-angiotensin system is very important in elevating blood pressure in a substantial proportion of patients who have essential hypertension.[50] It has been proposed that measurement of plasma renin activity as a function of urinary sodium excretion would allow categorization of hypertensive patients according to the degree that enhanced vasoconstriction or plasma volume expansion was contributing to the rise in blood pressure. In this proposed vasocon-

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striction-volume analysis,[50] patients with high renin activity have a vasoconstrictive hypertension because of excess activity of the pressor hormone angiotensin II and patients with low renin activity are hypertensive due to plasma volume expansion of uncertain cause. Patients with normal renin activity have elements of both volume expansion and vasoconstriction operating. Some investigators, however, have found this categorization of renin subgroups to be poorly reproducible in cases of essential hypertension.[51]

To probe the utility of such a scheme in predicting response to antihypertensive drugs, investigators have studied the blood pressure response in the renin subgroups to drugs that decrease volume or renin activity. The prediction that renin-lowering drugs such as propranolol hydrochloride would be most useful in subjects with high renin activity and that diuretics would be most efficacious in patients with low renin activity was validated by these studies.[52] It should be noted, however, that β-adrenergic-blocking drugs and diuretics have major antihypertensive properties unrelated to their effect on renin or volume. Thus, Woods and coworkers[53] found no difference in low-renin and normal-renin patients in their antihypertensive responses to the diuretic chlorthalidone compared with propranolol.

It became clear that to resolve this question more specific probes of the renin-angiotensin system were needed. Initially, analogues of angiotensin II were developed that exhibited the properties of competitive antagonists against the action of angiotensin II. The analogue saralasin acetate, which has been most extensively used in humans, is a peptide and must be administered intravenously. It is highly specific in its action. That is, it blocks blood pressure responses to infused angiotensin II but does not affect the response to other pressor agents such as norepinephrine.[54] Theoretically, then, this agent should block the effect of circulating angiotensin II and show the degree to which angiotensin participates in raising blood pressure. Indeed, patients with high renin activity, including many but not all patients who have renovascular hypertension, show a blood pressure fall when saralasin is administered.[54] Subjects with normal renin generally show little change in blood pressure.

Does this mean that hypertensive patients with normal renin activity do not have an angiotensin-dependent component to their blood pressure elevation? Not necessarily, for low-renin patients who have hypertension often have pressor rather than depressor responses to saralasin. This has been interpreted to mean that the analogue has intrinsic agonist or pressor properties.[55] When angiotensin receptors are not occupied, saralasin will cause a pressor response; when they are fully occupied by angiotensin (high renin states), the displacement by saralasin will lower blood pressure. But when the receptors are partially occupied (normal renin) both effects occur. The net result is that the use of saralasin tends to lead to an underestimation of the contribution of angiotensin to blood pressure maintenance. To compensate for this, saralasin is generally

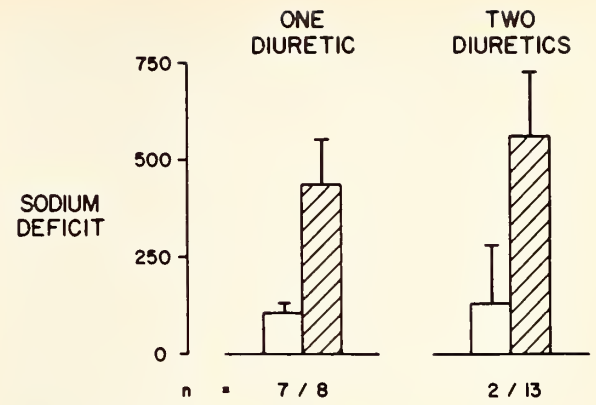

Figure 4.—Sodium deficit (in milliequivalents) achieved during diuretic administration in patients with essential hypertension undergoing saralasin administration. Hatched bars are saralasin responders; open bars are nonresponders. (Reprinted with permission from the American Heart Association and Thananopavarn et al.[56])

used following diuretic administration. Volume depletion tends to increase the relative contribution of angiotensin to blood pressure regulation. However, the precise degree of volume depletion necessary to offset the agonistic activity of saralasin is not known. We found that of 15 hypertensive men, none responded with a blood pressure drop when they did not take medications for four weeks but 8 had response after five days of diuretic therapy (metolazone, 5 mg daily) and 13 had response after spironolactone was added (400 mg daily) for five days.[56] Furthermore, the responders tended to have greater sodium losses to diuretic than the nonresponders (Figure 4). Thus, diuretic therapy, if given in sufficient amounts for long enough periods, will convert most hypertensive patients to saralasin responders. In addition, patients are heterogeneous in their natriuretic response to the same dose of diuretics. This makes it difficult to standardize the saralasin test as a direct measure of the degree of participation of angiotensin in essential hypertension.

The latest and perhaps most exciting advance in probing the renin-angiotensin system has been the development of converting-enzyme antagonists. These agents inhibit the activity of the enzyme that removes a dipeptide from angiotensin I to form angiotensin II. The initial compounds were isolated from the venom of a pit viper and a nonapeptide was synthesized. This material required intravenous administration, but subsequent and remarkable chemistry resulted in the development of an orally active drug, captopril.[57] Administration of this compound results in promptly reduced circulating angiotensin II and aldosterone levels.

Theoretically, the depressor response to this drug should correlate with the level and importance of angiotensin II in maintaining blood pressure. In hypertensive patients blood pressure initially falls, then rises and then falls again during continued captopril therapy.[58] Although the mechanism of this triphasic blood pressure response is unclear, it would appear that the initial and chronic depressor effects of captopril correlate well

with blood pressure dependency on the renin system. Thus, patients with high renin activity had the greatest fall, but subjects with normal renin also showed significant decreases. This provided further evidence that angiotensin II plays a role in normal-renin as well as high-renin hypertension.

Once again, things are not that simple, as it is now evident that captopril has multiple mechanisms of antihypertensive action. Many investigators have not found a close correlation between renin activity and blood pressure response to captopril.[59] Other hypotensive mechanisms for the action of converting-enzyme inhibitors must be considered. For years it has been known that this enzyme is also involved in the degradation of vasodilatory kinins so that inhibition of converting enzyme might increase kinin concentrations in the blood or in the kidney. In addition, there is evidence that vasodilatory prostaglandins may be stimulated by captopril. Moore and associates[60] showed that administration of inhibitors of prostaglandin synthesis blunts the hypotensive action of captopril. This mechanism may be particularly relevant to the hypotensive response seen in some low-renin patients.[61] Even normotensive subjects who have a normal sodium intake may show a significant fall in blood pressure with administration of captopril. Interestingly, this fall was completely blocked by indomethacin, a prostaglandin-synthesis inhibitor, but the fall seen after a low salt diet and the administration of captopril was not altered by indomethacin.[62]

It should be remembered that both angiotensin II and aldosterone levels are lowered by converting-enzyme inhibitors and both may play a role in blood pressure control. This is shown by some recent studies in hypertensive rat models. In spontaneously hypertensive rats, a significant fall in blood pressure follows inhibition of converting enzyme. This response is prevented by replacing adrenal steroids. In the one-clip, two-kidney hypertensive rat model, however, the hypotensive effect of captopril was not altered by steroid replacement.[63]

It is also conceivable that captopril has actions within the resistance vessels that are distinct from its effects on circulating angiotensin levels. Antonaccio and Kerwin[64] showed that captopril administration to spontaneously hypertensive rats decreased the vascular response to nerve stimulation. They hypothesized that in blood vessels local production of angiotensin may be important to the action of norepinephrine released by nerve stimulation. This local angiotensin formation could be decreased by captopril.

It would appear that converting-enzyme inhibition lowers blood pressure by mechanisms in addition to the decrease in angiotensin II levels. Although the ideal probe of the renin-angiotensin system may not have been found, the search has strengthened the position that this system is important in essential hypertension and has provided us with promising classes of therapeutic agents.

Heterogeneity of Renin-Angiotensin System

Peter Eggena, PhD:* Although the renin-angiotensin system has been extensively studied,[65,66] many questions about its role in blood pressure homeostasis remain unanswered. Renin, an enzyme of renal origin, cleaves renin substrate, a protein of hepatic origin, to generate the decapeptide angiotensin I.[67,68] Angiotensin I-converting enzyme rapidly cleaves the decapeptide to produce the octapeptide angiotensin II.[69] This peptide hormone is known to contribute to blood pressure control via at least three pathways—direct vasoconstriction,[66,70] volume control via aldosterone[66,71] and by centrally mediated mechanisms.[72] Recent studies have indicated, however, a greater complexity of the system than originally assumed. Renin has been found to be heterogeneous with respect to enzyme activity and physical chemical properties[66,73-75] and several forms of renin substrate having different kinetic variables have been reported.[76-78] In this review I will address the recent discovery of inactive reninlike enzymes and the multiple forms of renin substrate (angiotensinogen) found in plasma of normotensive and hypertensive animals and in humans.

Renin

A significant additional increase in plasma renin activity is observed following preincubation of plasma with certain proteolytic enzymes,[79,80] exposure to acid pH[80,81] or storage at −5°C.[82,83] This additional reninlike activity has been termed inactive renin or prorenin. Not enough evidence is available to show that activated enzyme is a biosynthetic precursor of renin. Likewise, neither qualitative nor quantitative differences are seen in inactive renin patterns in normal and hypertensive persons.[84] The kidney may be a source of inactive renin[85] but in the anephric state other tissues can release inactive renin into the circulation.

Of major physiologic importance is whether inactive renin can be converted to the active form in the plasma of normal humans. Numerous in vivo studies have been done to acutely or chronically[86-89] stimulate or suppress active renin levels in plasma and measure resulting changes of inactive renin. Several investigators have reported reciprocal relationships between active and inactive renin,[86,90] whereas others have shown that the plasma level of inactive renin is not influenced by dynamic changes in active plasma renin.[88,91] Two recent studies have suggested that contrary to the hypothesis that inactive renin is a biosynthetic precursor of active renin, inactive renin may in part represent a partially degraded form of active renin, due to the natural process of renin catabolism.[92,93] Inactive renin appears to be heterogeneous and no significant differences are evident when comparing normal and hypertensive subjects, which argues against a role for this enzyme in the genesis of human hypertension. Because inactive renin is observed in anephric subjects and in arterial tissue, it is tempting to speculate that this enzyme may be a

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tissue enzyme similar to tonin,[94] capable of locally controlling vasoconstriction. Plasma levels of inactive renin may be a spillover product of the tissue enzyme system and therefore would not be responsive to dynamic alterations in plasma renin levels that originate from the kidney. In light of the seemingly contradictory findings, it is difficult to assess the physiologic control of inactive renin production or its role in blood pressure regulation.

Renin Substrate

Renin substrate, or angiotensinogen, essential for angiotensin generation, was originally thought to be present in plasma in such high concentrations that it could never be a rate-limiting factor for the generation of angiotensin. Recent kinetic studies have taken exception to this hypothesis. The Michaelis-Menten constant (K_m) of the renin reaction under normal physiologic conditions is about equal to the plasma concentration of renin substrate (Table 1). Therefore, under normal conditions the renin reaction proceeds at half the maximal rate. For the renin reaction to be independent of renin substrate concentration would require the renin substrate concentration-to-K_m to exceed 5. Table 1 shows that substrate to K_m ratio under several physiologic and pathologic conditions never exceeds 2.5. Renin substrate is therefore almost always rate limiting in the generation of angiotensin, but no statistically significant differences in renin substrate concentration have been found between normal and hypertensive subjects.

Renin substrate is heterogeneous in its molecular forms with respect to electrophoretic and immunologic properties. A high molecular weight form of renin substrate is found in women who have estrogenic hypertension, and the total renin substrate level may be elevated (Table 1). Similar findings were noted in the plasma of normal and hypertensive pregnant women at term (Table 1). Comparison of ethinyl estradiol with conjugated equine estrogens shows that ethinyl estradiol is more potent in stimulating the high molecular weight form of renin substrate.[95] This high molecular weight form has a higher affinity for renin than normal renin substrate, thus causing an accelerated rate of angiotensin I production in estrogenic hypertension. These studies suggest that in addition to measuring total renin substrate when assessing the plasma renin system of a person, one should also determine which forms of renin substrate are present.

The recent discovery of all of the components of the renin-angiotensin system in the central nervous system[72] and arterial tissue[84,96] suggest local generation of angiotensin II and possible control of blood pressure that is not evident from simply measuring plasma renin activity. This point of view is further strengthened by the recent observation that blood pressure can be lowered in hypertensive persons who have no apparent abnormality of the plasma renin system, by drugs that block the conversions of angiotensin I to angiotensin II.[97] All of the described studies show an unexpected complexity in the renin-angiotensin system, but also seem to clearly indicate that this system, when fully elucidated, may play a significantly more important role in blood pressure regulation than originally imagined.

Body Weight, Hormones and the Development of Hypertension

JAMES R. SOWERS, MD:* The relationship between obesity and hypertension has been recognized for decades. The association of excessive weight and high blood pressure probably has its inception in children and adolescents.[98,99] Yet the relationship between increasing age and hypertension also appears to be specific for affluent urban populations in whom there is increasing body weight with age.[100,101] Furthermore, reducing weight reduces blood pressure in both normo-

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TABLE 1.—*Michaelis-Menten Constants (K_m) and Renin Substrate in Human Plasma*

	Physiologic and Pathologic Conditions	*K_m ng AI per ml*	*Renin Substrate ng AI Eq per ml*	*High Molecular Weight Substrate Percent*	*Substrate to K_m Ratio*
1	Healthy ♂ (n=13)	1,573±436	1,957±222	0.0	1.2
2	Essential hypertension (n=12)	1,551±575	1,459±235	0.0	1.0
3	Renovascular hypertension (n=6)	1,523±661	1,822±440	0.0	1.2
4	Hypertension associated with uremia (n=4)	1,354±360	2,595±610	0.0	1.9
5	♀ on estrogen therapy, normotensive (n=20)	2,610±190*	5,150±1,530*	3.4	2.0
6	Estrogenic hypertension (n=5)	3,320±720*	6,800±2,450*	7.3	2.0
7	Term pregnancy plasma pool (n=2)	4,150	10,170	12.0	2.5

AI=angiotensin I

*Significantly elevated from 1 through 4.

tensive and hypertensive persons.[102-105] Several hemodynamic and hormonal mechanisms may explain why obesity leads to elevated blood pressure and how weight reduction lowers it. Increased total blood volume and cardiac output in the presence of normal peripheral vascular resistance are found in obese patients who have hypertension.[106] When these measurements are corrected for body surface area, however, investigators could not find differences between obese and nonobese hypertensive patients.[107] Salt restriction has also been suggested as a more important factor than caloric reduction in the lowered blood pressure associated with weight loss in obese patients.[108] However, recent studies have shown that weight loss is associated with reductions in blood pressure independent of salt intake (Figure 5).[103,104] Our group has observed that obese patients who have hypertension have higher supine plasma norepinephrine and epinephrine levels and greater norepinephrine responses to upright posture and isometric handgrip exercise than nonobese persons (Figure 6).[105] Plasma norepinephrine correlates with blood pressure levels in obese patients before weight loss and reductions in blood pressure are accompanied by reductions in plasma norepinephrine levels.[109]

Fasting and hypocaloric protein diets are associated with a natriuresis during the early days of caloric deprivation.[110-112] This natriuresis has been attributed to hyperketonemia,[110-111] relative hyperglucagonemia,[112] relative hypoinsulinemia[111-112] and mineralocorticosteroid resistance.[112] The natriuresis associated with hypocaloric diets could also result from alterations in catecholaminergic influences on electrolyte excretion in the kidneys. Circulating epinephrine and norepinephrine can cause reabsorption of sodium independent of changes in renal hemodynamics.[113,114] Dopamine also influences the regulation of renal sodium excretion, producing a natriuretic effect.[115-116] Our observations that during early caloric deprivation plasma dopamine level increases while epinephrine and norepinephrine levels decline[105,109] suggest that these alterations could affect renal catecholaminergic influences on electrolyte excretion and account for the natriuresis.

Weight and blood pressure reductions in obese patients on a hypocaloric diet are also associated with a fall in plasma renin activity and aldosterone levels.[104,105] There also appears to be a temporal relationship between the reduction in norepinephrine and the changes in renin activity during weight loss. Because the sym-

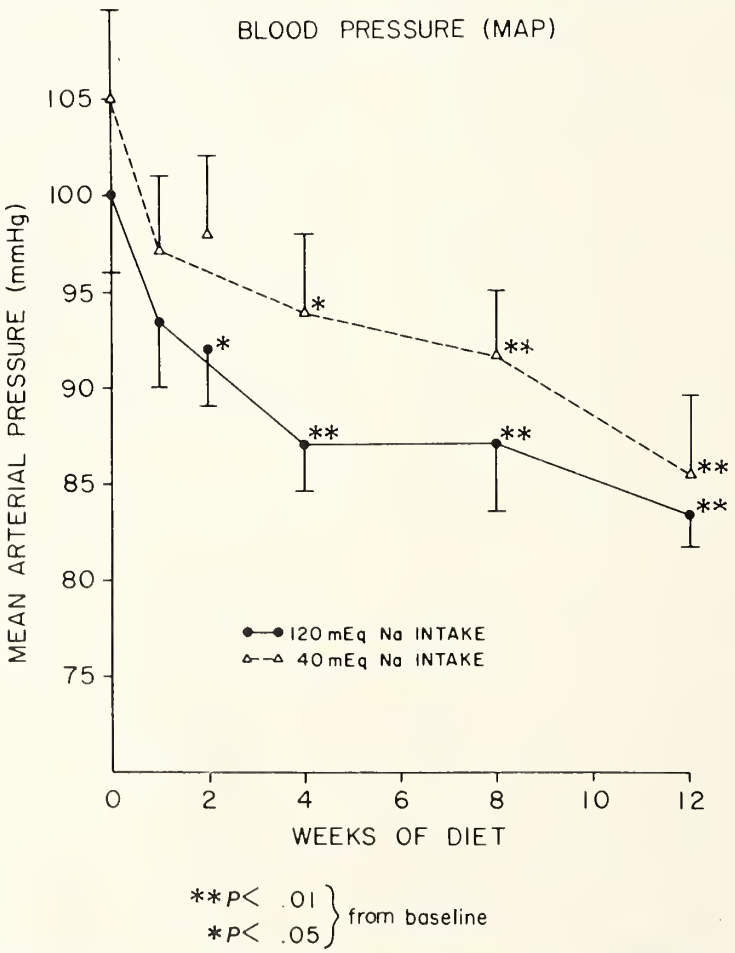

Figure 5.—Reductions in mean arterial pressure during 12 weeks of extreme caloric restriction in obese patients on two sodium-intake regimens (from Tuck et al[104]). mmHg = millimeters of mercury, Na = sodium.

pathetic nervous system is an important factor modulating renin release, reductions in renin with caloric deprivation and weight loss could reflect diminished sympathetic nervous system activity. Thus, the sequence of events leading to depressor responses with caloric restriction in obese patients may result from initial effects on plasma catecholamines and secondary effects of reduced adrenergic activity on renal sodium excretion and the renin-angiotensin-aldosterone system.

A defect in the transmembrane sodium fluxes and a high intracellular sodium concentration have been reported in cells from experimentally hypertensive animals and in humans with hypertension as previously detailed. Obesity is also associated with increased erythrocyte intracellular sodium levels and reduced numbers of sodium-pump units as quantitated by ouabain binding and sodium-potassium-adenosine triphosphatase-mediated rubidium uptake.[117] A reduction in the level of sodium transport and higher intracellular sodium content have been described in liver and muscle from obese (ob/ob) mice.[118-120] We have recently examined the relationship between reduced sodium transport and blood pressure maintenance in obesity. Similar to other reports, there was reduced erythrocyte Na^+, K^+ ATPase activity in obese patients compared with nonobese controls (Figure 7).[121] Cation transport, as measured by ^{86}Rb uptake by erythrocytes, was also reduced in parallel with the decrease in Na^+, K^+ ATPase activity. There was a negative correlation between pump activity and ^{86}Rb uptake versus the percentage of excess over ideal body weight. Although Na^+, K^+ ATPase activity and ^{86}Rb uptake by erythrocytes increased and intracellular sodium concentration decreased during 12 weeks of caloric restriction and weight loss, levels still remained abnormal compared with the nonobese controls (Figure 7). Importantly, however, there was no correlation of blood pressure with intracellular erythrocyte sodium levels or with the measurements of erythrocyte pump activity throughout the study. This negative relationship between erythrocyte pump activity and blood pressure in obesity would not support the concept that membrane transport abnormalities are the leading factor elevating blood pressure in obesity.

These observations offer evidence that several metabolic derangements associated with obesity contribute to the associated hypertension. These include increases in sympathetic nervous system activity, the renin-angiotensin system and certain aspects of disturbed

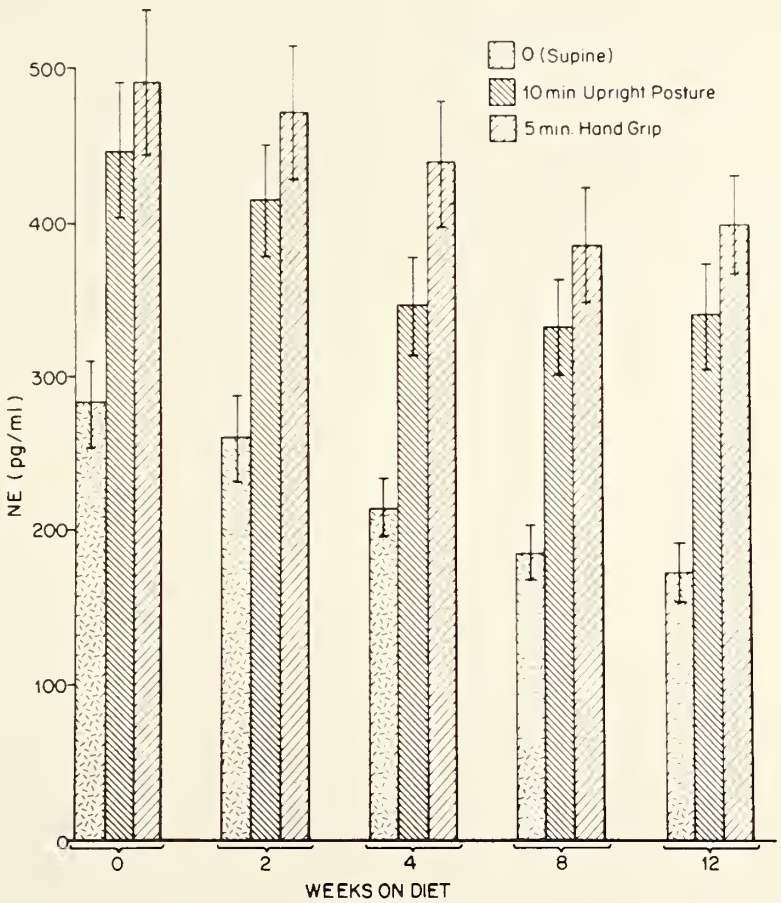

Figure 6.—Mean (±standard error of the mean) plasma norepinephrine (NE) responses to ten minutes of upright posture and five minutes of isometric handgrip exercise during weight reduction in obese patients on extreme caloric restriction (from Sowers et al[105]).

carbohydrate metabolism that may alter renal sodium excretion.

Newer Antihypertensive Drugs

MORTON H. MAXWELL, MD:* Several new antihypertensive drugs that directly attack the previously described hormonal systems in hypertensive persons have recently been approved for clinical use in the United States. These include the following: (1) atenolol (Tenormin), a β-adrenergic-blocking agent; (2) captopril (Capoten), a converting-enzyme inhibitor, and (3) calcium entry blockers, nifedipine (Procardia), verapamil (Calan, Isoptin) and diltiazem (Cardizem).

Atenolol

Atenolol has a unique profile in that it is relatively cardioselective and lipid-insoluble compared with other β-blockers.[122] A high binding affinity for the cardiac β_1-receptors should in theory result in fewer adverse side effects of β-blockers that are related to inhibition of peripheral β_2-receptors, such as asthma or cold extremities. Drugs that are lipid-insoluble have a longer plasma half-life and duration of action, permitting once-a-day dosage, and, because of their limited entry into the brain, may cause fewer central nervous system side effects such as sleep disturbances and abnormal dreams. Metoprolol tartrate (Lopressor) is also cardioselective but is lipophilic and has a shorter duration of action. Nadolol (Corgard) also has a long duration of action but is not cardioselective. All available β-blockers appear to have equal antihypertensive efficacy.[123] The flat dose-response curve and long duration of action of atenolol permit once-a-day dosing, and its relative cardioselectivity, especially in low doses, may benefit some patients. β-Blockers are widely used in Europe as step-one antihypertensive drugs. Because of their antiarrhythmic and cardioprotective properties, they will probably be used more frequently as monotherapy in the United States.

Captopril

Captopril inhibits the enzyme that converts angiotensin I to angiotensin II and inactivates bradykinin. Decreased circulating angiotensin II relieves arteriolar vasoconstriction and decreases aldosterone secretion, thereby lowering blood pressure and preventing sodium retention; increased bradykinin levels also tend to reduce blood pressure by other mechanisms.

The place of captopril in antihypertensive therapy is unclear. The occurrence of such side effects as taste disturbances and skin rash, as well as the more serious complications of membranous glomerulopathy and bone marrow suppression, may have been related to the large doses used (up to 500 mg per day). In mild to moderate hypertension, captopril is as effective as a diuretic or an adrenergic inhibitor, with very few adverse effects.[124] It is particularly effective in high renin forms of severe hypertension, such as renovascular hypertension or scleroderma.[125] Its antihypertensive effect is potentiated by diuretics and vasodilators. Black patients who have hypertension, perhaps because of lower renin levels, have been found to respond less well to captopril than white patients with hypertension.

In the package insert, it is stated that the use of captopril is restricted to patients with severe hypertension who have not responded to other antihypertensive drugs. With the use of smaller doses (12.5 to 25 mg twice a day), captopril will likely be useful as step-one therapy in moderate hypertension, with a diuretic added as step two if necessary.

Calcium Entry Blockers

Vascular smooth muscle contraction depends on intracellular calcium concentration. Several drugs of dif-

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Figure 7.—Mean (±standard error of the mean) erythrocyte membrane sodium-potassium-adenosine triphosphatase (Na^+-K^+-ATPase) activity in nonobese subjects and in obese subjects during 12 weeks of weight reduction by extreme caloric restriction. (Data taken with the permission of *Clinical Science* and redrawn from Sowers et al[105]).

TABLE 2.—*Comparison of Calcium Entry Blockers*

Characteristics	*Relative Effects*		
	Nifedipine	*Verapamil*	*Diltiazem*
Circulatory			
Systemic resistance	↓↓↓	↓↓	↓↓
Heart rate	↑↑	N	N
Atrioventricular conduction	N	↑↑	↑
Cardiac output	↑↑	↑ or ↓	↑ or N
Side Effects			
Hypotension and facial flushing	+++	++	0
Headache and dizziness	++	++	+
Atrioventricular block	0	++	0
Heart failure	0	+	0
Constipation	0	++	0
Nausea and vomiting	++	+	0
Edema	+	0	0

↓=slightly lowered, ↓↓=moderately lowered, ↓↓↓=greatly lowered, ↓↓↓↓=very greatly lowered, ↑=slightly raised, ↑↑=moderately raised, N=no change, +=mild, ++=moderate, +++=extreme, 0=no effect.

fering pharmacologic configuration have the common property of inhibiting the slow calcium channel entry into arterial smooth muscle cells, thus reducing peripheral vasoconstriction and lowering blood pressure.[126] In keeping with the premise that increased intracellular calcium and sodium concentrations may have a primary pathogenic role in hypertension, the calcium entry blockers have little or no effect on the arterial pressure of persons with normal blood pressure.

The presently available calcium entry blockers have been extensively studied in ischemic heart disease and atrial arrhythmias and have thus far been approved by the Food and Drug Administration for use in only those conditions. Nevertheless, their use in the treatment of hypertension will likely become widespread before official approval.

It should be reiterated that the presently available calcium entry blockers do not share a common site of action or have similar configurations and thus have important clinical differences on cardiac performance, vascular contractility and side effects (Table 2). The common effects that these drugs have on the circulation include reduced arterial pressure, reduced heart rate (unless reflex tachycardia occurs) and decreased inotropic state of the myocardium that may be concealed by reflex changes in the heart rate, and reduced oxygen requirements of the heart. Like the β-blockers, they may prevent cardiac arrhythmias and myocardial reinfarctions, which would make them most appropriate in treating hypertensive patients who have coronary artery disease.

The following is the frequency of side effects reported in large series[126] of patients: 17% for nifedipine, the drug being discontinued in 5% because of intolerance; 9% for verapamil, with discontinuation in 1%, and 4% for diltiazem, with rare discontinuation. Thus diltiazem has the fewest side effects, but also is the least effective antihypertensive agent. Congestive heart failure and atrioventricular conduction defects are contraindications for verapamil, as is concomitant therapy with other myocardial depressants, such as β-blockers and disopyramide. Nifedipine may be used safely in patients taking β-blockers and in patients with left ventricular dysfunction. In the near future, the most widely used calcium entry blocker for hypertension will likely be nifedipine.

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Medical Staff Conference

Osteoporosis

Part II. Prevention of Bone Loss and Fractures in Women and Risks of Menopausal Estrogen Therapy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *In the first part of this symposium on postmenopausal osteoporosis, Dr Henry Genant described the important advances made in quantifying bone density in vivo. Now Dr Gilbert Gordan will discuss the treatment—or, more accurately, the prevention—of this serious form of osteopenia. This is a topic to which Dr Gordan has devoted many years of clinical research and an area in which he has been a major contributor.*

DR GORDAN:† Osteoporotic fractures, occurring with little or no trauma, become extremely frequent in women after menopause or oophorectomy. It is now established from direct measurements of bone mass and from epidemiologic studies that the cause of this serious public health and human problem is estrogen deficiency. Formerly little attention was paid to osteoporosis, but now, with increasing longevity, especially in women, the magnitude, expense and—most important—the preventability of this disease are becoming evident. A prophylactic program is feasible to prevent this hazard to the largest growing segment of our population, elderly women.

Early Observations of Osteoporosis

Osteoporosis is an ancient disease that has only recently become a prominent public health problem, largely because of demographic changes in our population coupled with improved diagnostic methods and better health care in the population as a whole. There are many historical references to osteoporosis. In 1824, for example, Sir Astley Cooper noted from observations at autopsy that in old age "the bones become thin in their shell and spongy in their texture." In 1881 Bruns noted that after age 50, fractures of the wrist and hip occur much more frequently in women than in men. This observation perplexed him because fracture was equated with trauma, and in those days men certainly had more occupational exposure to trauma than did women. But in the 19th century this condition of frequent fractures and loss of height was merely a puzzling curiosity. Not very many women lived long past the menopause (the average age of natural menopause at 50 has remained almost constant in northern and western Europe and the United States for centuries). The major health hazards for women even as recently as 50 years ago were, of course, infectious diseases and the dangers of childbearing; maternal and infant mortality was high. Relatively few lived long enough to be afflicted with the degenerative diseases of the aged that now demand most of our care and attention. The phenomenal advances of modern medical research and health care, which many of us experienced firsthand, have produced dramatic shifts in our population. Americans today are living longer and are, on the average, healthier than ever before, but we are no longer a young nation. The consequence is an ever greater demand on our diminishing pool of health care resources. We are already faced with the difficult ethical dilemma of deciding which patients are to receive the very expensive new therapies made possible by our remarkably sophisticated medical research. Our emphasis now, more than ever before, must be to pay more than lip service to *preven-*

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tion of disease, whenever this is possible, rather than focusing almost all of our attention on treatment.

Elderly women comprise the fastest growing group in our population. American women today outlive men by about ten years and can expect to live 40% of their lives after menopause. The human female is the only mammal that outlives reproductive capability. Socially, elderly women are an important and valuable resource with the potential for high productivity to the community as long as they are not impaired by degenerative disease. Few of the degenerative diseases of aging are preventable, but an important one, postmenopausal osteoporosis, is potentially so.

Racial and Sexual Characteristics

It is now established that white-, yellow- and brown-skinned women lose bone rapidly after menopause, so that by age 70, these women have on the average lost 50% of their peripheral cortical bone mass. While black women do lose some bone with aging, this loss is small compared with other ethnic groups and when imposed on a denser skeleton rarely produces pathologic osteoporosis. The mechanism of this genetic protection enjoyed by black women is not yet known; we do know, however, that black women have a much lower incidence of fracture and when fractures occur they are almost exclusively associated with significant trauma.

The sexual dimorphism of bone loss is pronounced. Men of all races at all ages have denser skeletons than women and bone density parallels skin color: black men having the most dense bones and white women the least. Drs Silvia and Eric Meema, in a study of white men in Toronto, Canada, showed that men do not have significant age-related bone loss until around age 70 and the relatively few men in their study who survived to age 95 lost only about 25% of the normal adult male bone mass.[1] In contrast, these authors and others have shown that bone loss in women starts much earlier in life and is biphasic. There is a rapid loss in the first six to ten years after natural menopause—earlier in the case of women who have had oophorectomies—and then a slower, progressive rate of bone loss thereafter. Thus, women who start out with less dense skeletons begin losing bone quite early in life, have a rapid acute phase of bone loss following loss of gonadal function and then continue to lose bone slowly for the rest of their life. Women with a natural menopause at around age 50 can now expect to live another 32 years. It follows, therefore, that unless prophylactic measures are taken to prevent or arrest this inexorable wasting of the skeleton, most women can also expect during the postmenopausal period to lose, overall, 1% to 2% of their peripheral cortical bone each year and much greater amounts of axial bone mass. By age 80, a third to two thirds of the entire skeleton has irretrievably disappeared.

The clinical importance of bone loss of this magnitude is that with enough time (more critical for younger women undergoing bilateral oophorectomy) the skeleton becomes so rarefied and fragile that it is not

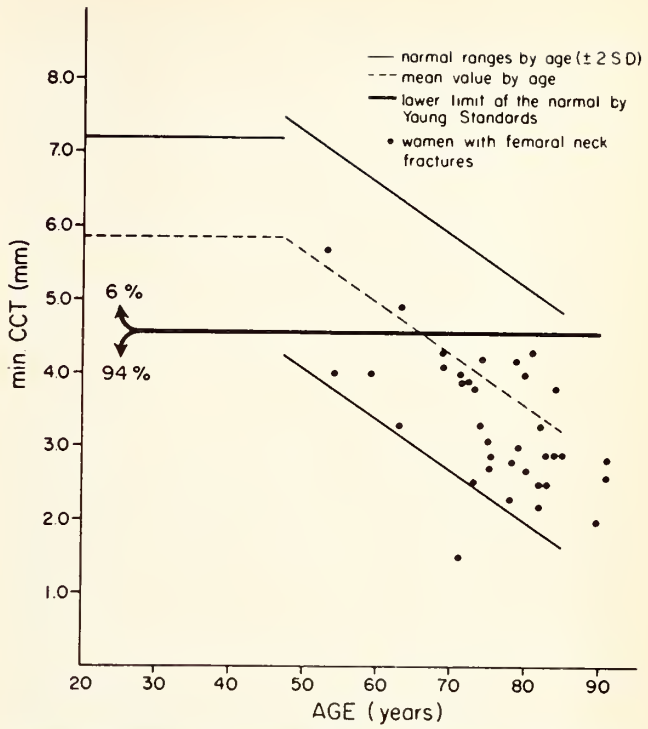

Figure 1.—Minimal combined cortical thickness (CCT) of radius in 36 women who had femoral neck fractures in relation to normal range (from Meema and Meema[1]).

capable of withstanding normal, or slightly increased, biomechanical stress. In these women vertebral compression fractures are common following a bumpy automobile trip or bending over to pick up a grandchild or even a sudden sneeze. The relationship between pathologic osteoporosis and hip fractures in elderly women is well documented. As shown in Figure 1, elderly women with hip fracture have all lost a significant amount of cortical thickness compared with average postmenopausal values. Some of these women have only 200 mg of hydroxyapatite per sq cm of bone remaining; this is contrasted with a normal value of 700 mg per sq cm found in younger women, which means a loss of more than two thirds of their total skeletal mass. We now see a continuity between what has been called "physiologic" bone loss, meaning that we all lose some bone with aging, and "pathologic" bone loss, because fracture is obviously pathologic. Or, as our patients have been telling us for years, "No, doctor, I did *not* fall down and break my hip; my hip gave way and I fell down."

Hip fracture is the ultimate insult to postmenopausal women, occurring usually after 20 or more years of insidious bone loss and vertebral deformity. In all but black women, the incidence doubles every five years after age 50, so that women in their 80s have a 40% chance of having sustained one or more hip fractures. Hip fractures are associated with a high incidence of morbidity and mortality. They do not heal spontaneously, require anesthesia and surgical repair and may result in complications of thromboembolism, pneumonia or congestive heart failure. Many of the patients,

though active before their fracture, never walk again. As the population of elderly women increases, patients who have hip fracture will continue to require ever greater amounts of health care resources for their medical and nursing care. The dollar cost of treating patients with hip fracture is now more than $1.4 billion a year, most of it paid by Medicare funds. The US Vital Statistics on hip fracture have been available only in the past three years; they show that two thirds of the deaths resulting from hip fracture occur in white women over the age of 65. In short, hip fractures cause more deaths than handguns. The good news is that the bone loss that causes most hip fractures is preventable; deaths from handguns are a much more difficult problem to solve. Three case-control studies show that estrogens protect against hip and wrist fractures in elderly women.[2-4] Protecting these women against skeletal fragility not only prevents a painful, disabling disease but saves society billions of dollars in health care and rehabilitation costs. I often think when I listen to politicians talk about our country's need to cut costs in medical care that this would be an excellent place to start. Of course, a billion dollars may not seem like very much compared with a defense budget of $239 billion but, as the late Senator Dirksen pointed out, "a billion here, a billion there, and the first thing you know, you're talking about real money."

Dr Genant noted that the important underlying cause of fractures—bone loss—is now readily and accurately measurable by noninvasive techniques. The precision of the computed tomographic scanning technique is a distinguished contribution to the early detection of postmenopausal bone loss. In a study from Copenhagen, derived from 315 healthy women in early menopause, Christiansen and co-workers have shown that peripheral bone loss precedes fracture by nine or ten years.[5] Dr Genant's measure of vertebral spongiosa steepens the slope of bone loss by a factor of 7 so that it is now feasible, for the first time, to detect insidious, painless bone loss in persons years before fractures occur, just as we recognize and treat glaucoma before optic atrophy and blindness, or diagnose and treat hypertension to prevent myocardial infarction or stroke.[6]

The earliest complication of postmenopausal bone loss is crush fractures of weight-bearing vertebrae. These fractures cluster after age 50 and are associated with statistically significant loss of peripheral bone measured in the radius, while the vertebral spongiosa is visibly depleted. You see women with vertebral crush fractures everywhere. They are bent over with kyphosis, walking painfully with a wide base, desperately edging their way through the traffic of San Francisco, Honolulu, London or Tokyo. In fact, all ethnic groups are represented except blacks. I would like to emphasize the importance of loss of height as a diagnostic factor. Accurate height measurement is best obtained with the simplest equipment—a tape measure tacked to the wall and any rigid object such as a chart, book or ruler used as a right angle. The important thing is to have the patient, without shoes, stand as straight as she can, heels together and her head level. Women who have had vertebral compressions may have twinges of back pain that are worrisome to them and to their doctors because this may indicate another fracture. Each vertebral crush fracture is usually associated with a loss of 1 cm or more of height. Therefore, if there is an accurate baseline height, an additional fracture is easily excluded without the expense of x-ray films or unnecessary exposure to radiation. It is useful, therefore, when one first sees a woman with osteoporosis to estimate her previous height, both from her memory and from comparison of her height with measurement of her arm span. The famous drawing by Leonardo da Vinci, known as the Canon of Proportions, shows his fascination with the following statement of Vitruvius Pollio in *De Architectura,* written about 26 BC: "If we measure from the sole of the foot to the top of the head, and apply the measure to the outstretched hands, the breadth will be found equal to the height." Except in healthy black persons (who have long arms and legs) or in patients with hypogonadism or arachnodactyly, this relation is usually valid within half an inch. A word of warning, do not rely on stadiometers attached to weight scales; these are often quite inaccurate. In patients with vertebral crush fractures, precision of measurement is essential both to estimate previous height loss and to evaluate therapy. Effective treatment prevents further loss of height.

The Importance of Estrogen in Bone Loss

The most important study showing the importance of estrogen in preventing bone loss after oophorectomy in younger women was reported by Lindsay and associates in 1976.[7] In this study the bone mass of 120 women was measured by photon absorptiometry in the metacarpal bones at two sites. Using a double-blind technique, 63 of the women were given mestranol, 20 μg daily (the amount found in the lowest dose oral contraceptives in this country), and 57 were given a placebo. The women taking the placebo lost bone steadily throughout the first five years of the study, whereas the women taking mestranol were protected. This study is being continued. At the end of ten years it was found that the placebo-treated women continued to lose bone mass, had an average height loss of 1.5 cm and showed evidence of vertebral wedging. In contrast, the estrogen-treated women at ten years had the same bone mass as at the beginning of the study, had not lost height and showed no evidence of vertebral wedging. This is a nonintervention study. In contrast, in our studies we do not merely observe bone loss; we use a crossover design so that when a woman has lost a significant amount of bone, she is advised to cross over to an effective dose of estrogen.

Bones do not contain estrogen receptors, therefore, it is a point of considerable theoretical interest how estrogens affect bones. Klotz at l'Hôpital Beaujon-Clichy in Paris was the first to point out in 1975[8] that calcitonin levels in postmenopausal women and in

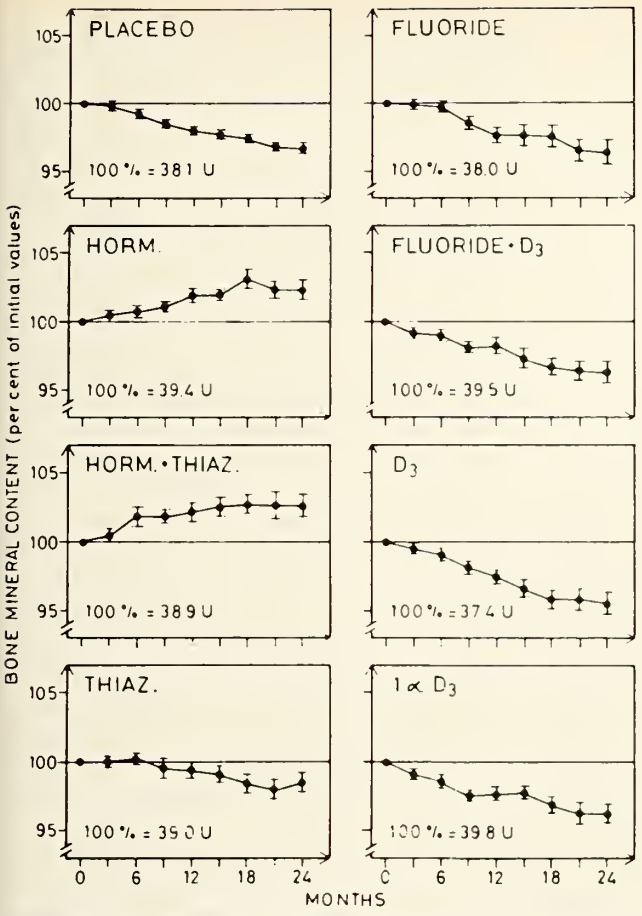

Figure 2.—Bone mineral content measured by photon absorptiometry of distal forearm in 315 healthy women 0.5 to 3 years after last menstrual period (from Christiansen et al[5]). Horm = hormones (estradiol, 4 mg, plus estriol, 2 mg, plus norethisterone acetate, 1 mg, in 28-day cycles); fluoride = sodium fluoride, 20 mg daily; D_3 = vitamin D_3, 2,000 IU a day; $1\alpha D_3$ = 1 α-hydroxyvitamin D_3, 0.25 μg daily; all subjects also received calcium gluconate to provide 1 gram of calcium a day.

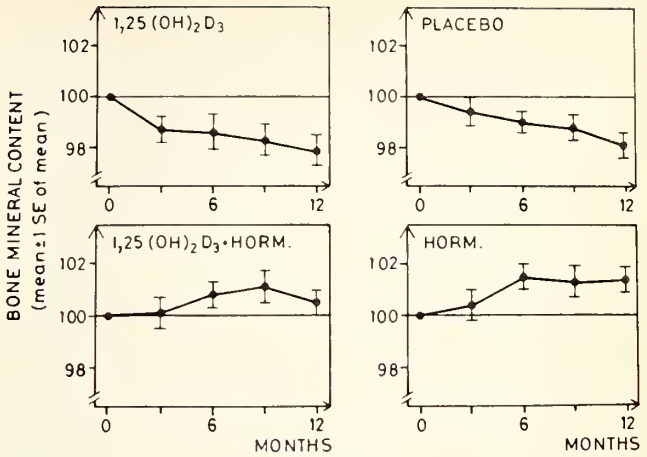

Figure 3.—Changes in bone mineral content (photon absorptiometry of distal forearm) during one year of therapy in 92 normal women 2.5 to 5 years after last menstrual period (from Christiansen et al[14]). Horm = hormones (estradiol, 4 mg, plus estriol, 2 mg, plus norethisterone, 1 mg, in 28-day cycles); 1,25 $(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3, 0.25 μg daily; all participants also received 500 mg of calcium a day.

castrated rats are very low, and they can be raised by administering estrogen. This work has now been confirmed by Milhaud in Paris[9] and by Hillyard[10] and Stevenson[11] and associates in MacIntyre's laboratory in London. Another important mechanism is more controversial—activation of renal 1α-hydroxylase by estrogen. It has long been known that calcium absorption is poor in elderly women. The elegant studies of Heaney and associates[12] in Omaha show that calcium balance after the menopause can only be maintained by very large doses of calcium given orally, whereas estrogen-treated women remain in balance on much smaller dose regimens. Gallagher and co-workers have reported that serum 1,25-dihydroxyvitamin D_3 levels in postmenopausal women are low and that they rise to normal during estrogen treatment.[13] Stevenson and Christiansen have not been able to confirm these findings[5,11] but considering the difficulties with present measurements of 1,25-dihydroxyvitamin D_3, the matter is not closed. In any event, it is clear that estrogen-treated postmenopausal women maintain calcium balance at lower levels of calcium intake than untreated women.

A large number of studies have been carried out to see whether vitamin D, its metabolites and various other agents would prevent or reverse bone loss in postmenopausal women. Christiansen's extensive and careful studies have shown (Figures 2 and 3) that whereas the hormones estradiol and norethisterone acetate prevented bone loss equally well, vitamin D or 1α-vitamin D were not any better than a placebo, and neither 1,25-dihydroxyvitamin D_3 nor fluoride was of any value. I would also emphasize that the latter two are toxic. Adding 1,25-dihydroxyvitamin D_3 to either of the hormone therapies produced results not quite as good as either hormone alone while, of course, adding considerably to the cost of treatment and increasing the risk of hypercalciuria and hypercalcemia.[14]

Despite the volume of data now accumulated from various sources showing the efficacy of estrogen replacement therapy in maintaining skeletal integrity in the postmenopausal woman, a recent survey in the United Kingdom showed that whereas gynecologists consistently treat postmenopausal osteoporosis with hormones, only half the internists do.[15] In this country, gynecologists and family practitioners are receptive to the evidence that postmenopausal osteoporosis is the consequence of estrogen deficiency, whereas the internists are somehow more susceptible to the blandishments of vitamin D and fluoride. Frankly, I do not understand this.

Other Ways of Preventing Osteoporosis

I am often asked if exercise will prevent postmenopausal osteoporosis. While immobilization is obviously bad for bones and all other systems, there is no present evidence to show that exercise alone can replace estrogen for postmenopausal women. The recent findings

that some young women health enthusiasts become amenorrheic, lose bone and sustain fractures strongly suggest that exercise alone is not enough.

In preventing bone loss and fractures we should not overlook the importance of such safety measures as removing the well-named "throw" rugs, obstacle courses of electric wires or long telephone cords and similar hazards. In addition, installing grab bars in bathtubs and showers, sturdy handrails on stairways and good lighting helps prevent falls and minimize trauma. We also tell elderly osteoporotic patients not to pick up heavy objects such as shopping bags or suitcases, to limit themselves to lifting items weighing less than 4.5 kg (10 lb) and to get accustomed to using a shopping cart or similar device not only for shopping but also around the house and garden. Rearranging kitchens and work patterns can also do much to minimize bending and can reduce backaches.

There are four salient, independent risk factors for osteoporotic fractures: being female, lacking gonadal function, not being black and not taking antiosteolytic agents which include estrogens, gestogens, calcium, anabolics or calcitonin. Smoking cigarettes contributes indirectly to osteoporosis by causing an earlier menopause and decreased body fat. Leanness is a contributing factor because adipose tissue contains aromatase that converts the adrenal androgen, androstenedione, to estrone. No one is advocating obesity, however; fat may be good for bones but it is bad for longevity. Our image of the typical osteoporotic patient is a lean, small-boned woman. This is partly because thin women have low blood estrone levels and because there just are not many old fat women.

The prevalence of bone loss in postmenopausal women and women who have had oophorectomies is clearly shown in our study in which 30 of 31 women who received less than 0.6 mg of conjugated estrogens daily lost a significant amount of vertebral spongiosa.[6] Clearly, in these younger women (less than 50 years of age) the risk factor was loss of gonadal function. In this study we found that the minimal effective dose of conjugated estrogens, 0.6 mg, protected five of six women. Christiansen in his study of women who had a natural menopause has also obtained a dose response to estradiol cycled with norethisterone acetate.[4] Those taking the placebo lost bone, 1 mg of estradiol a day reduced the rate of bone loss, 2 mg daily produced a slight gain in bone mass and 4 mg daily produced a greater gain. The optimal protective dose in this study, therefore, was 2 mg daily of estradiol. The Scottish women in Lindsay's study who gained a very small amount of bone mass in their first five years of estrogen replacement therapy did not maintain that gain in the next five years. They did, however, maintain their premenopausal, pretreatment values.[7] You cannot replace much bone tissue after it is lost, hence the importance of *prevention* in postmenopausal osteoporosis.

We have shown in a long-term study, with follow-up for more than 30 years, that pathologic osteoporosis can be arrested and further fractures prevented, even when the disease is far advanced. This has only been shown with full replacement doses of estrogen—that is, 1.25 mg of conjugated estrogens, or 50 μg of ethinyl estradiol, or 1 mg of stilbestrol or 6 mg of methallenestril for 21 to 25 consecutive days each month. We also recommend adding a progestin for the last ten days of the estrogen cycle, with a hiatus of five to seven days each month without hormones. On this regimen we prepare our patients to expect a period of withdrawal bleeding for three to five days during the time they are not taking the hormones. Our experience with compliance has been excellent, largely because from the start we take the time with each of our patients to explain the rationale of treatment and what they can expect and we encourage them to ask questions. Patient education is an essential part of the treatment.

Although the ideal treatment of estrogen deficiency is replacement with oral estrogens in the lowest effective dose, it is clear that not all women can or should receive estrogen therapy. Clear contraindications are, of course, a history of breast cancer or invasive endometrial cancer, bleeding uterine fibroids, migraine or congestive heart failure. The most common reason for women refusing estrogen replacement therapy is cancerphobia, which is primarily caused by sensational and often inaccurate or incomplete reports in the mass media. Fortunately for our patients, we now have good data to show that bone loss can be prevented by several other methods: progestational agents; large doses of calcium taken orally, anabolics or frequent injections of calcitonin. With this information, we now have ample ways to prevent postmenopausal bone loss and women need no longer be condemned to osteoporotic fractures of the vertebrae, wrists and hips.

Because of experience with very large doses of estrogen in former contraceptive pills or for treatment of prostatic cancer, it was feared that postmenopausal estrogen replacement would also increase the risk of myocardial infarction or stroke. Recent studies, however, show that the doses used for postmenopausal replacement therapy actually *reduce* this risk. In fact, estrogen-treated women have only 43% the risk of dying of myocardial infarction that occurs in comparable, but untreated, women.[16] The recent Lipid Research group study of the National Heart, Lung, and Blood Institute, National Institutes of Health, showed that the overall mortality of estrogen-treated women is only 37% of that found in untreated comparable women, in part because of a rise in protective high-density lipoprotein levels.[17]

I have long advocated estrogen replacement therapy for menopausal women to prevent vaginal atrophy, dyspareunia, bone loss with deformity and fractures and, in general, to add life to years. It is now also apparent that this treatment adds years to life.

DR SMITH: *Dr Gordan has given us a persuasive summary of the evidence that estrogen therapy can prevent the progressive bone loss characteristics of postmeno-*

pausal osteoporosis and therefore prevent its severe and often life-threatening complications. But what of the dangers of long-term use of exogenous estrogens? Dr Philip Hoffman will review this important topic for us.

Risks of Menopausal Estrogen Therapy

DR HOFFMAN:* Since 1977 the Food and Drug Administration has required that every woman given a prescription containing estrogen be given an information sheet describing the possible complications of estrogen therapy.[18] The most important of these are listed in Table 1.

There is no doubt that estrogen taken in sufficient doses for enough time at the appropriate age can cause all of these complications in women. The pertinent issue, however, is the risk incurred by a woman receiving estrogen in doses appropriate for preventing osteoporosis.

The incidence of cholecystitis is increased 2.0-fold to 2.5-fold by either oral contraceptive or menopausal estrogen therapy.[19] The other disorders listed in the table appear in roughly the order of our epidemiologic knowledge about them, the information on endometrial carcinoma being the most extensive.

Endometrial Carcinoma

A postmenopausal woman's risk of endometrial carcinoma developing is about 1 in 1,000 per year. Beginning in 1975 a series of published retrospective studies estimated the relative risk of endometrial carcinoma for women using estrogen to be 2 to 18 times that of nonusers.[20-23] Horwitz and Feinstein have argued that much of the apparent increased risk is attributable to more complete ascertainment of cancers in women undergoing dilatation and curettage for uterine bleeding than in largely uninvestigated control patients, but still found a relative risk of about 2.0.[24] In a recent series of 9,000 autopsies, endometrial carcinoma was four to five times as common as would have been expected in living patients, giving support to the contention that using controls from whom biopsy specimens were not taken overestimates relative risk.[25]

Accepting that postmenopausal estrogen administration does increase the risk of endometrial carcinoma, what does getting the cancer mean for a patient? For most women, it will mean a dilatation and curettage procedure, a hysterectomy and considerable physical and psychologic pain. For a few it will mean radiation therapy. The death rate has been studied by Collins and associates in 860 women, a third of whom had taken estrogen.[26] The five-year survival for those who had taken estrogen was 92% and for nonusers survival was 68%. Comparison with the appropriate age-specific survival rates for the general population of women indicated that the five-year survival rate for the estrogen-using cancer patients was virtually the same as for noncancer patients, whereas the survival for women who did not take estrogen was considerably less than for women of the same age at large. In another study, survival among estrogen-using cancer patients was actually significantly better than in the general population of the same age.[27]

Most of the improved survival among estrogen users is due to their tumors being better differentiated and less advanced. Whether this advantage is due entirely to earlier detection through better surveillance or to some other difference is not known.

In 1975 Gambrell started a prospective study of women being treated with sex hormones for menopausal symptoms.[28,29] To date more than 25,000 woman-years have been recorded. The women have largely chosen their own therapy from several options, and surveillance has been excellent (Table 2). In this study, the relative risk of endometrial carcinoma attributable to taking estrogen was about 2.0, as in the most optimistic retrospective studies. The most striking data, however, are those indicating that giving cyclic progestin along with the estrogen not only eliminated the increased risk of cancer due to estrogen, but actually decreased it below that found in untreated women. This observation has been confirmed by several independent reports, including a ten-year double-blind prospective study started in 1971.[30]

The treatment regimen recommended by Gambrell consists of giving estrogen for the first 25 days each month. A progestin is added on the 16th day and continued through the 25th day. No hormones are given between the 26th day and the end of the month. The usual estrogen dose is 0.6 mg of conjugated estrogens or 20 μg of ethinyl estradiol daily. Either norethindrone acetate, 5 mg, or medroxyprogesterone acetate, 10 mg, may be used as the progestin. Smaller doses of progestin would likely be equally satisfactory, but to obtain the degree of protection against endometrial carcinoma shown in Table 2, the progestin must be used for at least ten days each month.

Progestin probably diminishes the endometrial cancer risk by causing a virtually complete slough of the endometrium each month, thus preventing hyperplasia and

TABLE 1.—*Risks of Estrogen Therapy*

Endometrial carcinoma	Subarachnoid hemorrhage
Breast cancer	Thromboembolism
Ischemic heart disease	Cholecystitis

TABLE 2.—*Incidence of Endometrial Cancer**

Therapy	*Patient-Years*	*Cancers*	*Incidence Per 1,000*
Untreated	2,477	6	2.42
Estrogen	2,302	10	4.34
Estrogen-progestin	7,063	5	0.71

*Adapted from Gambrell.[29]

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TABLE 3.—*Incidence of Breast Cancer in Postmenopausal Women**

Therapy	*Patient-Years*	*Cancers*	*Incidence Per 1,000*
Untreated	3,799	19	5.00
Estrogen	10,028	15	1.37
Estrogen-progestin	7,332	7	0.96

*Adapted from Gambrell.[29]

TABLE 4.—*Total Number of Deaths in Postmenopausal Women**

Treatment	*Patient-Years*	*Deaths*	*Incidence Per 1,000*
Untreated	9,386	63	6.71
Estrogen	3,401	9	2.65

*Adapted from Bush et al.[17]

neoplasia. Most postmenopausal patients will have light withdrawal bleeding with this regimen, creating a significant clinical management problem, but one that patient education can usually overcome.

For patients who find monthly withdrawal bleeding unacceptable, the extreme alternative of giving unopposed estrogen is not as great a risk as has been previously supposed. It is one that is defensible for a well-informed, well-monitored patient. The risk of dying from endometrial carcinoma if the progestin is omitted is certainly less than 0.4 per 1,000 per year and the total death rate is probably not significantly greater than for the general population, assuming any bleeding is investigated immediately.

Breast Cancer

Literally hundreds of papers have been written about the risk of breast cancer and estrogens. Breast cancer kills about 36,000 women in the United States each year, whereas endometrial cancer currently kills about 3,000, very few of whom have ever taken exogenous estrogens. A modest increase in the risk of breast cancer that would be difficult to prove in even a large study might be of extreme clinical importance. The relative risk of breast cancer due to menopausal estrogen therapy has been estimated in retrospective studies to range from 0.7 to 3.4, with most estimates clustering about 1.0. The highest estimated risks have usually been in small subsets of larger populations and the computation of confidence limits almost never included corrections for multiple comparisons.[31]

The only large prospective study with which I am familiar is Gambrell's study of the same cohort of women discussed with regard to endometrial cancer.[29]

The risk of 5 per 1,000 per year observed in the untreated population (Table 3) is close to the expected baseline rate for the postmenopausal population studied. The use of estrogen, with or without progestin, significantly diminished the occurrence of breast cancer. Other known risk factors were examined and could not account for the results. The primary weakness of the study is its relatively short duration, the maximum follow-up being nine years.

In summary, the current state of knowledge of the effect of menopausal estrogen replacement on breast cancer risk is that there are some prospective data that suggest a protective effect. Retrospective studies have not indicated that the risk ratio is other than 1.0. A small but clinically important increased risk has not been ruled out, but seems unlikely.

Cardiovascular Disease

The compelling data linking exogenous estrogen to various forms of cardiovascular disease can be divided into the following two types: studies of oral contraceptives in premenopausal women and studies of high doses of diethylstilbestrol (DES) in old men. Premenopausal women have lower risks of ischemic heart disease than do men of the same age, and this difference disappears gradually after menopause. In fact, this observation provided the rationale for some of the male diethylstilbestrol studies.

The doses of estrogen required for prevention of osteoporosis are smaller than those contained in oral contraceptives, and much lower than the equivalent doses of diethylstilbestrol studied in men.[32] The doses used for menopausal therapy have virtually no impact on clotting factors and have never been shown to have any effect on thrombotic phenomena.[19,33] The little that has been published on the effect of menopausal estrogen on stroke tends to show (but certainly does not prove) that treated women have fewer strokes.[34]

What has been shown is that conjugated estrogens in doses used for prevention of osteoporosis lower low-density lipoprotein and very low-density lipoprotein cholesterol while raising high-density lipoprotein (HDL) cholesterol (especially the HDL-2 fraction [density, 1.063 to 1.125 grams per ml]) in postmenopausal women.[29,35-37] Moreover, estrogen replacement in these doses seems to lower blood pressure slightly and decrease body weight.[38,39] Whether these reductions in risk factors translate into lowered risk of ischemic heart disease has yet to be proved, but evidence is growing that they do. Bain and associates found the relative risk of nonfatal myocardial infarction to be significantly reduced by the use of replacement estrogen among women who had had oophorectomies.[40] In a retrospective case-controlled study, Ross and colleagues found that the relative risk of fatal ischemic heart disease among postmenopausal women taking estrogen compared with controls was 0.43 (95% confidence interval, 0.24 to 0.75).[41] In a recent prospective report with an average of just over five years follow-up, Bush and co-workers found the age-adjusted risk of death from all causes for estrogen users among women aged 40 to 69 was only 0.37 (95% confidence interval, 0.17 to 0.79) times that for nonusers (Table 4).[17] Among women who had had oophorectomies, the protective effect of estrogen was even greater.

Conclusion

As the benefits of postmenopausal estrogen therapy for prophylaxis against osteoporosis become more ob-

vious, reassessment of the risks of such therapy is necessary for a physician to care appropriately for postmenopausal patients. Current data suggest that exogenous estrogen in doses appropriate for prevention of osteoporosis increases the risk of endometrial carcinoma less than was previously thought and does not increase the risk of dying from the disease. Moreover, the increased risk can be abolished by administering progestin. Estrogen therapy does not appear to increase the risk of breast cancer or cardiovascular disease, and there is preliminary evidence that treating women with estrogen may reduce age-specific mortality.

To help women make informed decisions about estrogen replacement therapy, a physician must place the well-publicized but often negligible risks of estrogen therapy in proper perspective and balance them against the substantial benefits such therapy provides.[42]

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Epitomes
Important Advances in Clinical Medicine

Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Male Reproductive Hazards

In 1977 workers in a California pesticide plant noted the few number of children fathered by employees in a specific department. There were no abnormal physical or laboratory findings except for extremely low sperm counts. Now seven separate studies have been completed on male workers who were exposed to dibromochloropropane (DBCP). Although the data are still incomplete, about 15% of men exposed to dibromochloropropane are azoospermic and another 21% are oligospermic. These observations have led to an explosion of interest in chemical and environmental agents that affect sperm and the agents currently known to affect male reproduction have recently been summarized by Whorton in this journal.

Despite the importance of studying male reproductive function, little is known about screening procedures for known and potential hazards. With a high vasectomy rate, an aging work force and variable sperm assay procedures, it has become increasingly difficult to define a "normal" sperm count. Alcohol and cigarette smoke may provide a background of abnormal findings difficult to separate from those of toxic exposure. Questionnaires for monitoring male workers for fertility have been proposed by Levine and others. Although such methods might be valid for severe reproductive toxins such as dibromochloropropane, their validity for evaluating more subtle changes must be studied further.

Male reproductive hazards can also cause loss of libido, impotence, testicular anatomic abnormalities or alteration of seminal secretions—all of which can be missed when only sperm is analyzed. As more information is reported, it is remarkable to note the increasing number of factors affecting sperm. These include nutrition, temperature, vibration and noise exposure, antisperm and antibodies. Another concern is the possible transplacental hazards of drugs or chemicals such as diethylstilbestrol (DES) on developing male testes. Clear cell adenocarcinoma of the vagina in adolescent girls has been described in female offspring of DES-treated mothers. Transplacental effects of diethylstilbestrol on testes have also been reported. Interactions of chemicals, drugs and environmental factors must be studied for a clear understanding of the significance of work-place exposures.

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Reproductive Hazards in the Workplace

The role of occupational exposures is receiving increasing attention in medical literature. Whereas patient histories contain detailed information about medications, smoking and alcohol consumption, information concerning possible workplace exposures to lead, mercury, solvents, pesticides, heat, radiation and biologic agents is usually absent or vastly inadequate.

Research in recent years has expanded the concept of the "at risk" worker, which previously focused on the traditional blue collar trades. Today workers in agriculture and service occupations, including those in

hospitals and laboratories, are being studied. Numerous investigators during the past decade have reported an increased incidence of spontaneous abortions and birth defects among female operating room personnel. The increased frequency of congenital malformations in the offspring of male anesthetists heightened interest in the impact of a father's occupational exposures on reproductive outcome. The latter findings have since been shown in other epidemiologic studies and supported by extensive studies in animals. The offending agent in the case of operating room personnel was believed to be anesthetic gases. Rather than excluding workers, measures were instituted using engineering controls to eliminate the gases.

The waste anesthetic gas studies increased awareness of the wide spectrum of reproductive outcomes of workplace exposures: menstrual irregularities, infertility, miscarriages, birth defects, stillbirths, low birth weight, increased infant and childhood morbidity and mortality, including growth retardation, and mild-to-profound intellectual deficits or emotional disturbances.

Toxic exposures may initiate damage before conception or during early pregnancy when an embryo is considered particularly vulnerable to either lethal or developmental effects. Exposures may have effects throughout pregnancy, for instance on the central nervous system, because the brain continues to develop throughout pregnancy and well into the first year of life. Breast-feeding in the case of a working mother is of concern; recent evidence has documented the presence in mothers' milk of pesticides, metals, solvents and other toxic materials from workplace and other environmental sources, occasionally at levels higher than accepted limits for cows' milk.

Clinicians should obtain occupational histories from both parents when exploring problems related to infertility or adverse pregnancy outcomes.

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Prevention of Cement Allergy

DERMATITIS RESULTING from allergic contact sensitivity to dichromate is uncommon among cement workers, but when it occurs it may be severe and persistent, frequently necessitating loss of a job and rehabilitation. Since 1950 this form of dermatitis has been known to be caused by minute amounts of hexavalent dichromate found in cement. It is important to differentiate this type of dermatitis from the irritant dermatitis that is experienced by cement workers from time to time and is caused by the alkalinity and hygroscopic nature of cement.

Since the 1920s it has been recognized that conversion of hexavalent chromium to the trivalent form eliminates allergenicity almost completely. Recently Fregert in Sweden introduced a practical, simple way to reduce the hexavalent chromium in wet cement at the workplace immediately before its use. The method consists of adding small amounts of ferrous sulfate in an aqueous solution to the cement during the final mixing before it is poured. When used as recommended, the preparation in no way alters the characteristics of the resulting concrete.

Large studies of this procedure are in progress in Europe; it has not been used to any extent in the United States, however. The method is especially useful for small projects such as tile setting, where workers add the ferrous sulfate solution to the mix as the work progresses.

Because chromate cement dermatitis is a serious disease for which no effective treatment or preventive measures have been found, adding ferrous sulfate may prevent the development of new sensitizations to dichromate and reduce the severity of recurrences in persons already sensitized.

ROBERT M. ADAMS, MD

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Return to Work After Myocardial Infarction or Coronary Artery Bypass Operation

MORE THAN 500,000 persons survive myocardial infarction or coronary artery bypass operations in the United States each year. While those with persistent, severe physical impairment rarely return to work, most survivors are capable of reemployment. Many persons with little or no residual physical disability, however, return to work slowly or not at all. Several investigators have explored this phenomenon and have recommended therapeutic measures to enhance resumption of work.

Factors associated with delayed or no return to work include low educational level, advanced age, depression and maladaptive coping styles. Personal, local and national economics and cultural expectations further influence return-to-work patterns. Persons with an inappropriately pessimistic view of their medical prognosis have a low probability of returning to work. This is especially true when he or she attributes the cardiac event to job stresses. Less studied are the effects of self-confidence and self-efficacy.

A person's history and perception of prior work are also important. Self-employed persons consistently return to work earlier than others, regardless of the physical and emotional demands of their job. Those doing blue collar work for others have the slowest return to work rate. Those who perceive job stress, lack of job

autonomy or other types of job dissatisfaction take their time returning to work.

Other persons often affect a patient's decision. Fear within the family and consequent alterations of family dynamics are particularly important. Employers may operate from fear and an exaggerated sense of liability in refusing to consider options for their workers who have had myocardial infarction or coronary artery bypass. Unions and governments may impose restraints in certain occupations. Lack of insurance coverage and reimbursement may preclude participation in cardiac rehabilitation programs that could speed recovery and reemployment.

Recommendations to improve return to work rates include active counseling by a physician during and after the hospital stay. Exercise testing of cardiovascular and peripheral function should be followed immediately by exercise prescription, including specific advice on home and work activities. Careful assessment of a patient's attitudes and beliefs regarding prognosis, job stress and the safety of work resumption allows a physician and others to plan appropriate physical and behavioral interventions. Most persons will benefit from participation in a comprehensive outpatient program that integrates emotional support and nutritional counseling with exercise. Careful monitoring by the program team and primary physician should identify persons "at risk" for delaying returning to work. Appropriate interventions can be planned to encourage work resumption, thereby minimizing the economic and emotional consequences of the infarction or operation.

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The Importance of Atopy in Occupational Skin Disease

THE TERM "atopy" refers to a hereditary condition in which asthma, hay fever and a specific type of chronic, recurring dermatitis are found, either singly or together. Atopic disease is estimated to occur in up to 25% of the population of the United States.

Dermatologists and occupational physicians have long suspected that atopy is prominent in the background of persons with occupationally related skin disease. Recently Shmunes and Keil, in conjunction with the South Carolina Industrial Commission, reviewed all cases of compensated skin disease recorded in that state during a one-year period, 1978 to 1979. The total number of cases was 958, representing a direct cost of $143,000 and 2,100 lost workdays due to an occupationally related skin disease.

The predominant diagnosis in 94% of the cases was contact dermatitis and the hands were involved in 81% of those cases. The upper fifth percentile was responsible for 68% of the total fees and 77% of the lost time.

The investigators found that 82% of the affected workers were atopic. Assuming the frequency of atopy in the general population to be as stated above, the relative odds of an occupational skin disease developing are 13.5 times greater if a worker is atopic.

This finding emphasizes the importance of a preplacement history to identify atopic workers who are likely to be susceptible to environmental factors that aggravate (or bring to clinical activity) atopic dermatitis. Such factors include excessive or unprotected contact with soaps, detergents, acids, alkalis or solvents; excessive heat and cold with rapid changes in environmental temperature; rough clothing against the skin; excessive and repeated friction and pressure, and probably also unusual emotional stress.

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Mycosis Fungoides and Occupation

THE SEARCH continues without interruption for occupational causes of cancer. Mycosis fungoides is a skin cancer that for years may hover between malignancy and nonmalignancy before an unequivocal diagnosis of cancer can be made. Despite major advances during the past decade in our understanding of this disorder, no etiologic agent has yet been found. Cohen and associates studied in detail the occupational backgrounds of 59 persons who had this disease and found that persons employed in manufacturing or construction jobs were at significantly greater risk (relative risk, 4.3). Furthermore, patient survival was reduced for those with industrial backgrounds.

Whether these findings will lead to an occupational—perhaps a chemical—origin for this unusual disease cannot be known without indepth studies that involve large groups of patients. The possibility is a challenge for further investigation.

ROBERT M. ADAMS, MD

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The Pregnant Worker

IT IS ESTIMATED that almost a million women workers become pregnant in the United States each year. An increasing number of these women are choosing to continue employment throughout most of their pregnancy. Moreover, more women than ever hold jobs in nontraditional fields. These and jobs in female-dominated "clean" industries often involve exposure to a multitude of chemicals or to strenuous physical activity. Recent

studies indicate that the physiologic adaptations of pregnancy enable a woman to maintain her usual prepregnancy range of physical activity, though larger body size may increase fatigue in very late pregnancy. There is some evidence that work itself may be associated with increased risk of spontaneous abortion or low birth weight, though it is difficult to separate out socioeconomic differences that may be responsible for these findings.

Our knowledge of the relationship between occupational exposures and adverse reproductive outcome is extremely limited. Known effects of exposure to industrial chemicals span the entire reproductive cycle for both male and female workers. The possibility of transplacental carcinogenesis has now been shown, and the potential for behavioral teratogenesis or other more subtle postnatal abnormalities is becoming known.

More than 600 agents can cause congenital abnormalities in animals, though fewer than two dozen are proved human teratogens. The first trimester is the period of greatest risk from teratogenic exposures but the central nervous and urogenital systems continue to develop throughout pregnancy, thus extending the period of risk for these systems. Postnatally, lipid-soluble chemicals may be passed into breast milk and thus to a nursing infant.

Many companies have developed "embryofetal protection policies" that exclude a pregnant worker from high-risk assignments. Such policies may not provide adequate protection for the following reasons: diagnosis of pregnancy does not usually occur until the period of major organogenesis is nearly complete, maternal exposure to substances causing chromosomal damage or mutations in genetic material *before* conception may also increase the risk of adverse outcome and paternal exposures may alter the male germ cell to cause a defect in the conceptus.

Physicians should always take a thorough occupational history from a pregnant woman. Inquiry as to the father's occupation should also be made. Ideal protection from potentially adverse reproductive outcome due to occupational exposures can be achieved only by reducing exposure to safe levels for all workers, regardless of sex, or by allowing all workers the choice of transferring (without loss of pay) to a job without exposures while attempting to conceive and during pregnancy.

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Editorials

Public Health and Preventive Medicine

AT A MEETING of the Editorial Board some time ago it was recommended that the journal develop a series of timely articles on topics in public health and preventive medicine that would be of interest to practicing physicians. This was in response to an expression of interest in writing such articles from the health officers of the seven western states that are served by the journal. The series begins in this issue and is being coordinated by Donald O. Lyman, MD, of the Department of Health Services of California. We believe these articles will be a useful addition to the journal and will prove to be of interest to our readers. We look forward to this series which should authoritatively reflect problems and progress in public health and preventive medicine in the West.

THE EDITORS

Psoriasis

DR NICHOLAS J. LOWE, in this month's Medical Progress article, presents an excellent review of therapeutic regimens available for the management of psoriasis. It is appropriate that this subject be brought before the medical profession at regular intervals because there are millions of people in the United States who suffer from this tragic skin disease. Most people with this problem will have the characteristic and highly unpleasant red scaly patches off and on for a lifetime. When the open red, scaling blotches appear on exposed areas such as the hands, arms and face it becomes a severe psychological burden to the sufferer. Unfortunately some physicians tend to discount the disease and not to give full and proper attention to a patient who asks for help. The art of medicine is most important in managing people with this problem.

As Dr Lowe points out in his article, there are numerous forms of treatment used in attempts to control this disease but there are no medications that cure it. Unfortunately, all medications that will give partial or complete relief from the signs and symptoms of the disease will do so only while they are being used and the disease recurs quite rapidly upon stopping the treatment. The most widely used group of drugs are the topical glucocorticoids because they are reasonably effective in suppressing the lesions without the staining, stinging or stench associated with many other topical drugs. However, glucocorticoids are far from perfect for therapy because frequently psoriatic lesions will recur during treatment and it is often observed that the lesions are worse after treatment with glucocorticoids has been terminated—a so-called rebound phenomenon.

In the past ten years there has been a great deal of interest in the management of psoriasis with psoralen plus ultraviolet light (PUVA), as is discussed by Dr Lowe. This is quite effective in controlling psoriatic lesions but again does not cure them; they recur quite rapidly after PUVA treatment is stopped. Also there have already been reports of cutaneous malignancies resulting from the use of PUVA and one might properly guess that in the future there will be many more malignant skin lesions induced by PUVA treatments. This unfortunate side effect of PUVA treatment should limit the use of this modality to specific circumstances, which will definitely limit the number of psoriatic patients who can receive PUVA treatment over a long period.

Any chemotherapeutic agent such as methotrexate can influence a psoriatic lesion because of the rapid turnover of epidermal cells in this disease. However, all of these internally administered chemotherapeutic agents have a myriad of unpleasant and occasionally disastrous side effects which again severely limit their use in the treatment of psoriasis. We are certainly handicapped by not knowing what the molecular mechanism is in the induction of psoriasis. Basic research in this disease is being done at many institutions and we can be hopeful that some understanding of its mechanisms will unfold and perhaps lead to a development of a more direct molecular method of controlling psoriasis.

One must always remember that psoriasis can undergo spontaneous resolution. This has, in the past, led many clinicians to the false impression that drugs they have given for this disease have been of some value when in fact they have not. The evaluation of any therapeutic agent in psoriasis must be done on a double-blind basis in a scientific manner. Practically every year someone publishes a new "cure" for psoriasis based on minimal anecdotal observations.

Our best hope is that basic research in cellular biology and the control of cell growth will lead us to a specific understanding of the molecular defect in psoriasis and from there to a specific mechanism for its control or cure.

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Will There Really Be Too Many Doctors?

THE CONVENTIONAL WISDOM now is that there are going to be too many doctors, especially by the 1990s and on into the next century. It is assumed that this excess of physicians will take care of any shortages or maldistribution that may exist and also that the expected increase in competition among physicians will result in lower costs for patient care. And no one seems to be feeling too sorry for the physicians who will supposedly

be in excess and presumably having a hard time making a go of it. But need this be the scenario or is it likely to be? No doubt there will be some changes in the distribution of physicians as they increase in number, and by choice many will work substantially fewer hours. This is already occurring. But even so will there really be too many doctors? Perhaps the same forces that brought about the former shortage will serve to increase the need for physicians during the next few decades.

Three categories of forces have been, are and will be active. First there is inexorable scientific and technologic progress in medicine and society as a whole which can only continue. Second, there are the social, economic and political forces engendered by the many and growing technologic, social, economic and political interdependencies resulting from this inexorable scientific and technological progress. And third, there will soon be another order of magnitude of technologic, social, economic and political interdependence as the forces of progress, specialization and the various resulting interdependencies find themselves interacting with increasing frequency within this closed biosphere that we call planet Earth. The intensity of all these interactions can only increase as science and technology continue to expand. And each of these categories of forces has its impact upon health and illness in humans and these kinds of effects fall within the special province of physicians and of the medical profession. One wonders if there will really be too many doctors or even if there will be enough to meet these even now foreseeable demands upon the only profession that is trained and authoritative concerning illness, injury and emotional disturbance in humans.

Many of these forces are the ones that have worked to get us where we are. Physicians have become specialized and interdependent in patient care. New technology enables us to do more for more people, albeit at greater cost. There are more people, and they are living longer and requiring more of our services. The better our services, the more of them are needed because people live longer with chronic ailments or, if cured, live on to contract yet another ailment needing care. All of this has increased health care costs and now issues of quality and costs are coming to the fore. Physicians are right at this economic interface in patient care and many of us are developing substantial expertise in the economics of health care. Some have even become something of specialists in this field. These growing interactions and interdependencies are also evident in an increasing prevalence of lawsuits involving health and patient care and in an all too manifestly evident expansion of legislative and political interventions in health affairs.

The future can only bring more of all of this. It is essential that the medical profession recognize that all of these technologic, social, economic and political developments impinge in one way or another upon health and illness in people and that all this therefore must become the business of the medical profession. There will be many new vistas and many new opportunities for physicians to develop new kinds of knowledge and new skills to practice effectively at these new interfaces of human activity which will occur in ever closer relationship to the realities of the closed Earth biosphere in what is biologically one world. There will be a need for new scholarship, for new kinds of research, for new education and training, and perhaps even a need for a selling or marketing of these many new professional roles. With all that there is to do, it hardly seems that there will really be too many doctors in this foreseeable future.

MSMW

Advances in Hypertension Research

THE FIVE CONTRIBUTORS to the Specialty Conference on hypertension in this issue are productive investigators in basic and clinical research. Their state-of-the-art reviews portray their intimate awareness of and participation in the rapidly expanding field of the treatment of clinical hypertension.

The following are a few comments about what is and what is not covered in this symposium. Dr Tuck provides a thorough look at the exploding research in cellular transport of sodium. All of us wish that these disparate observations could be meshed into a single explanation for the pathogenesis of primary (essential) hypertension. Dr Tuck avoids that temptation, though I and others have tried.[1] He provides interested clinicians with a detailed road map that should be of great help in following the developments that are sure to come in this area.

Drs Golub and Eggena give shorter reviews of what is happening in the world of renin. Though I do not share their enthusiasm for the probable role of renin-angiotensin in primary hypertension, their work and analyses are among the best and deserve careful reading.

Dr Sowers is obviously involved in exciting work, that of exploring the relationships between obesity and blood pressure that may be mediated by hormones and transport defects. As much as anybody and more than most, he should help us through the mess that has characterized most past research in this field.

Last but never least, Dr Maxwell provides brief updates on some new antihypertensive drugs. The longer I know Dr Maxwell, the more I respect his clinical judgment; and I share his enthusiasm for atenolol and calcium entry blockers and his reservations about captopril.

All in all, these short reviews are well worth reading because they provide interested clinicians with up-to-date and well-reasoned views about some of the current developments in hypertension research. We had all better pay attention—40 million hypertensive Americans are depending upon our knowledge.

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Case Reports

Wound Botulism Associated With a Positive Tensilon Test

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THE GREAT MAJORITY of human botulism cases occur after ingestion of food containing preformed toxin elaborated by *Clostridium botulinum*. Infrequently, these organisms can elaborate toxin following inoculation into a wound. We report a case of type A wound botulism in which a significant delay in diagnosis occurred because of a strongly positive response to edrophonium chloride (Tensilon).

Report of a Case

A 37-year-old man presented to a local emergency room because of a sore throat, headache, difficulty focusing his eyes, dizziness and generalized weakness. Treatment with phenoxymethyl penicillin (Pen-Vee K); brompheniramine maleate, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (Dimetapp Extentabs), and acetaminophen with codeine (Tylenol #3) was prescribed and the patient discharged. Over the next three to four days progressive dyspnea, dysphagia, ptosis and increasing bilateral arm weakness developed. The patient was seen at another local emergency room where an edrophonium chloride (Tensilon) test was done, resulting in pronounced improvement in grip strength and decreased ptosis. The patient was admitted to St Joseph Hospital, Eureka, California, with a tentative diagnosis of myasthenia gravis.

On physical examination the patient was noted to be markedly obese and had a blood pressure of 180/118 mm of mercury, pulse of 110, temperatures 36.8°C (98.2°F), weight 196 kg and respirations 26 and shallow. Pupils were 3 mm and reactive, and there was bilateral ptosis and extreme neck weakness. Breath sounds were decreased and a 4-cm abscess was present on the volar surface of the left forearm. Deep tendon reflexes were present, plantar responses were flexor and sensory examination showed no abnormalities. Further questioning of the patient elicited that seven to ten days before admission he had punctured his left forearm on chicken wire while attempting to clean out an unused chicken coop. Over the four to five days before admission the puncture site had enlarged, become reddened and very tender. He had not eaten home-canned food.

Laboratory studies showed a hemoglobin of 19.0 grams per dl and a leukocyte count of 6,900 per μl with a normal differential. Roentgenogram of the chest showed bibasilar atelectasis.

The patient became progressively hypoxic and hypercapneic and was subsequently placed on mechanical ventilation. Administration of prednisone and pyridostigmine bromide (Mestinon) was begun. The left forearm abscess was incised and drained and the patient was started on nafcillin, 2 grams given intravenously every six hours, pending cultures. Though aerobic cultures showed only coagulase-negative *Staphylococcus epidermidis,* anaerobic cultures four days later grew *Clostridium* spp, subsequently identified as *C botulinum*. The prednisone and nafcillin therapy was discontinued, and the abscess site was radically excised and treatment with aqueous penicillin G, 5 million units given intravenously every four hours, was begun. Serum for toxin studies was drawn and sent to the California Department of Health Reference Laboratory and two vials of trivalent ABE botulism antitoxin were administered to neutralize any residual circulating toxin. Toxin studies on the patient's serum were consistent with the presence of type A botulism toxin. Stool cultures were negative for *C botulinum*. Repetitive stimulation of the left median nerve, recording over the abductor pollicis brevis at rates from 1 to 3 Hz, failed to elicit any response, despite using a maximum strength stimulus for up to 15 seconds. A single maximal stimulus to the left peroneal nerve also failed to elicit any response.

The patient had a difficult hospital course, requiring tracheostomy and almost two months of mechanical ventilatory support. He required treatment for pneumonia and sepsis due to *Klebsiella pneumoniae,* as well as previously unrecognized hypothyroidism that undoubtedly complicated and prolonged his mechanical ventilation. He slowly regained strength and was discharged 61 days after admission.

Discussion

Wound botulism was first reported to the Center for Disease Control in 1943[1] and since that time 27 cases have been reported. Most (22) have occurred in men, perhaps reflecting a greater likelihood of injury or exposure. As in this patient, most previously reported cases were associated with type A botulism and more than a third of all cases have been reported from California.

Though some reports of cases have described no re-

Refer to: Edell TA, Sullivan CP Jr, Osborn KM, et al: Wound botulism associated with a positive Tensilon test. West J Med 1983 Aug; 139: 218-219.

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sponse to administration of edrophonium chloride (Tensilon),[2,3] others[4] have reported a positive response. This patient's abscess was incised and drained and a specimen of abscess cultured, but because there was a response to edrophonium chloride (Tensilon), radical debridement was delayed several days. Subsequent serum toxin studies were only strongly suggestive, but not diagnostic, of type A botulism, because detection of toxin in serum is most likely when studies are done closer to the onset of clinical symptoms.[3] In this particular patient the delay in diagnosis caused delay in obtaining serum for toxin studies. Subsequent mouse inoculation showed sublethal but clinically consistent illness in mice unprotected by monovalent type A antitoxin.

Disease entities of low incidence are not often considered in the early stages of a clinical syndrome. When clinical features of botulism are present in the absence of an implicated food product, clinicians should not be lured away from the diagnosis of wound botulism when a positive edrophonium chloride test (Tensilon) might suggest otherwise.

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Chronic Arsenic Poisoning Masquerading as Pernicious Anemia

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ARSENIC POISONING is a malady of protean manifestations that can affect the neurologic, hematologic, dermatologic and gastrointestinal systems.[1-3] A patient's presentation may be confusing, but the correct diagnosis, if considered, can be suggested by a simple, rapid, inexpensive and noninvasive screening procedure.

Report of a Case

A 64-year-old Hispanic man was admitted to another hospital because of two weeks of worsening mid and left upper quadrant abdominal discomfort. He had a history of mild adult-onset diabetes mellitus, but otherwise had no significant illnesses and was taking no medicines. He said he did not use alcohol excessively. Physical examination on admission showed no abnormalities.

Laboratory studies disclosed the following values: hematocrit, 29%; mean corpuscular volume, 91 cu μm, and leukocyte count, 1,900 per μl, with 48% neutrophils, 2% band cells and 43% lymphocytes (the rest of differential and platelet count not provided). A bone marrow aspirate and biopsy specimen showed megaloblastic changes, pronounced erythroid hyperplasia and a full range of myeloid maturation. These findings were interpreted as consistent with folate deficiency, and a regimen of low-dose folic acid replacement was begun pending blood levels and further evaluation.

No response was generated by the therapy. After several days in hospital, the patient began to have paresthesias in his hands and feet and difficulty walking. Neurologic examination at that time showed a profound loss of vibratory sense and proprioception in all four extremities and near-absent deep tendon reflexes. Although the folic acid and vitamin B_{12} concentrations in the patient's serum were in the low-normal range and no macrocytosis was noted on the peripheral blood smear, it was felt by the staff, in consultation with the hematology department, that this picture was most typical of pernicious anemia. A lumbar puncture showed no abnormalities except for mildly increased cerebrospinal fluid protein content. The first part of a Schilling test was done, which showed a decreased excretion of 2.6%. This result was interpreted as confirming the presence of pernicious anemia. Vitamin B_{12} was administered every other day, 1,000 grams intramuscularly, with five doses given before discharge. Because of the patient's continuing vague abdominal symptoms, other diagnostic procedures were done during his 16-day hospital stay—abdominal ultrasound, intravenous pyelogram, liver-spleen scan and barium enema. The only abnormal findings were decreased gastric motility and mild splenomegaly.

Upon discharge, the patient's anemia and neutropenia had substantially decreased, but his neurologic state was essentially unchanged. The discharge diagnosis was "probably pernicious anemia with severe neurologic manifestations."

One week after discharge, the patient presented to this hospital because of persistent abdominal pain and continued neurologic deterioration. He was unable to walk and barely able to stand. He also had near anesthesia in his hands, increasing muscular weakness and an inability to concentrate at times. On physical examination a hyperpigmented band was seen on his trunk and he had hyperkeratotic palms with several small, hyperpigmented macules on the digits. His fingernails appeared normal. There was a considerable loss of vibratory, proprioceptive, light touch and pinprick sensation distal to the elbows and knees, with a milder deficit extending to the trunk. His hand grip and wrist extension were significantly diminished in strength on both sides and he was barely able to lift his legs when

Refer to: Selzer PM, Ancel MA: Chronic arsenic poisoning masquerading as pernicious anemia. West J Med 1983 Aug; 139:219-220.

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supine. His stance was unsteady and he was unable to walk unaided. Deep tendon reflexes of the lower extremities were absent and those of the upper extremities were diminished.

A complete blood count showed a hematocrit of 33%, hemoglobin of 11.2 grams per dl and a leukocyte count of 4,900 per μl with 68% neutrophils, 4% band cells, 19% lymphocytes, 5% monocytes and 4% eosinophils. Platelet estimate was normal. Aliquots of urine were sent for heavy metal and porphyrin screens. The next day the test was reported as positive for heavy metals and suggestive of arsenic. A 24-hour urine specimen had an arsenic concentration of 0.55 grams per ml (normal <0.02 μg per ml, according to the Hine Laboratories, San Francisco). Lead and mercury concentrations were normal. For diagnostic confirmation, a large lock of scalp hair was shaved and sent for analysis in five sections. The most proximal section contained 45 μg per gram of arsenic (normal <0.3 to 0.5 μg per gram) and the distal sections were all within normal limits. These data suggested that the poisoning had occurred within four to five weeks, which is the average amount of time for 1 cm of hair growth, assuming a typical average daily growth of 0.35 mm.[4]

Both the peripheral blood smear and the bone marrow biopsy specimen from the other hospital were reviewed by our pathologists, who felt that all of the changes seen, including basophilic stippling on the peripheral smear and megaloblastoid forms, karyorrhexis and binucleated erythrocyte precursors in the marrow, were entirely consistent with the hematologic effects of arsenic.

Within six days of admission, the patient had been started on chelation therapy. He received 200 mg of dimercaprol intramuscularly every four hours for two days and was then changed to D-penicillamine, 250 mg given by mouth every eight hours. The urine was monitored for arsenic, which rapidly cleared within five days.

Although the patient felt better during his hospital course, there was little objective evidence of improvement. Electromyographic studies obtained several days after admission showed a polyneuropathy, with denervation limited primarily to the distal leg muscles. He received physical therapy in addition to medical treatment and was discharged to a nursing home for extended care. The source of the arsenic poisoning was not determined. Neither the home nor workplace showed any obvious environmental source, and the patient said he had not been exposed to pesticides or herbicides, contaminated seafoods, copper-smelting operations or wood preservatives. He took no home remedies or tonics and drank no illegal whiskey ("moonshine"). Attempted homicide was suspected but not proved.

Six months after discharge, the patient showed considerable improvement. He regained his ability to walk, but only with a wide-based gait. He still exhibited bilateral weakness of wrist and hip flexion and of foot dorsiflexion. Diminished sensation, particularly in the hands, persisted.

Discussion

Because of the multisystem involvement of chronic arsenic poisoning, the differential diagnosis is large and includes vitamin B_{12} deficiency, acute febrile polyneuritis (Guillain-Barré syndrome), Addison's disease, porphyria and poisoning from other heavy metals, particularly thallium.[1,2] The appearance of the peripheral blood smear in arsenic poisoning differs in several important ways from that in vitamin B_{12} or folic acid deficiency. In vitamin B_{12} deficiency, the erythrocytes are primarily normocytic and normochromic, and basophilic stippling is common; hypersegmented neutrophils are absent or rare, and relative eosinophilia may be seen. The bone marrow in arsenic poisoning may show occasional megaloblastoid forms but more typically is characterized by karyorrhexis and binucleated erythrocyte precursors.[2] All of these hematologic abnormalities except eosinophilia were present in our patient.

The neuropathy of subacute combined degeneration of the spinal cord that results from vitamin B_{12} deficiency may closely mimic that of chronic arsenic poisoning—that is, general weakness, glove-and-stocking paresthesias, loss of vibratory and position senses, unsteady gait and diminished deep tendon reflexes (initially).[5] A lack of parallelism between the hematologic and neurologic manifestations may arise from this vitamin deficiency. In our patient, however, the normal serum concentration of vitamin B_{12} and the normal mean corpuscular volume in the presence of profound hematologic and neurologic abnormalities could have suggested the correct diagnosis.

Summary

Except for the absence of white transverse bands on the fingernails (Mees' lines), this patient presented the classic signs of chronic arsenical poisoning—gastrointestinal complaints followed by profound peripheral neuropathy and concomitant hematologic and dermatologic changes. Because early, aggressive treatment with chelating agents may alleviate the effects of this toxin, a prompt diagnosis might substantially affect a patient's short and long-term prognosis.[3,6] This case shows the value of screening for heavy metals in evaluating gastrointestinal symptoms that are accompanied by pancytopenia or neurologic abnormalities.

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Normotensive Pheochromocytoma

Pharmacologic, Paraneoplastic and Anesthetic Considerations

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ALTHOUGH HYPERTENSION, sustained or paroxysmal, is usually a cardinal feature of pheochromocytoma, cases in which patients with this disorder were normotensive have been reported.[1-6] To extend further the clinical spectrum associated with this tumor, we describe a normotensive patient in whom fever of unknown origin, anemia, thrombocytosis, abnormalities of hepatic function and pronounced elevation of the erythrocyte sedimentation rate were the presenting features of a norepinephrine- and dopamine-secreting pheochromocytoma. Complete resolution of the fever and of the hematologic and biochemical abnormalities followed removal of this benign neoplasm.

Report of a Case

A 22-year-old black man presented to San Francisco General Hospital Medical Center on May 3, 1976, with a 13-month history of an 18-kg (40-lb) weight loss, fatigue, palpitations, night sweats, chest pain, epigastric discomfort and postexertional emesis. In the two weeks before admission, fever had developed. The family medical history was unremarkable.

Medical evaluation for the same symptoms seven and nine months before admission was remarkable for anemia, elevation of serum alkaline phosphatase level, reversal of albumin-globulin ratio and extreme elevation of erythrocyte sedimentation rate (Table 1). Serum protein electrophoresis showed a diffuse increase in gamma globulin values. A bone marrow biopsy specimen showed a reactive erythroid series with features typical of hemoglobin AC hemoglobinopathy and a reactive myeloid series indicating a chronic inflammatory state. Histologic examination of a liver biopsy specimen was interpreted as showing prominent dilated and congested central venous channels that suggested an early peliotic process. Findings of thyroid function tests, chest roentgenogram, pulmonary arteriography and cardiac catheterization were within normal limits.

On physical examination on admission to the medical service in May 1976, he was well developed, well nourished, slender and did not appear to be in acute distress. His recumbent blood pressure was 130/80 and 130/84 mm of mercury in the right and left arms, respectively, and his upright blood pressure was 140/80 mm of mercury. His heart rate was 92 beats per minute, respirations were 28 and temperature was 38.2°C (100.8°F). The precordial impulse was increased and a grade 2 systolic ejection murmur was noted. There was mild midepigastric tenderness when the abdomen was palpated.

The hematocrit ranged from 24% to 29%, the platelet count from 350,000 to 950,000 per μl and the leukocyte count from 10,800 to 12,800 per μl. The urine analysis and cultures of urine, blood and stool specimens showed no abnormalities. Findings of serum electrolyte and creatinine studies were normal. The previously noted abnormalities of hepatic function were still present (Table 1). The alkaline phosphatase was comprised exclusively of the liver fraction. Prothrombin time was 15.3 seconds, total bilirubin concentration was 0.7 mg per dl and serum aspartate aminotransferase (formerly glutamic-oxaloacetic transaminase) 42 IU per liter. Throughout the initial period of hospital stay, the patient had nervousness, headache and a crampy, occasionally severe, postprandial midepigastric pain. A weight loss of 5 kg over a five-week interval was recorded. A remittent fever, with daily temperature elevations between 38.0°C and 38.6°C, was noted. Skin tests yielded a positive reaction to dermatophytin control and negative reactions to purified protein derivative, histoplasmin and coccidioidin antigens. Lumbar puncture and an intravenous pyelogram showed no abnormalities. A double dose oral cholecystogram did not show the gallbladder and an intravenous cholangiogram with tomography failed to show the bile ducts and was interpreted as typical of hepatic disease. A gallium scan showed a possible intracolonic density in the left upper quadrant of the abdomen. Abdominal ultrasonography showed a normally functioning gallbladder and a 2- to 3-cm sonolucency to the right of the umbilicus. An abdominal arteriogram showed a solid hypervascular 6- by 7-cm left suprarenal mass suggestive of a neoplasm. The maximum blood pressure observed during the arteriogram was 160/100 mm of mercury and heart rate was 96 beats per minute. Computed tomography of the abdomen confirmed the presence of a left suprarenal mass.

On June 3, 1976, the patient was transferred to the General Clinical Research Center for preoperative evaluation. Preoperative and postoperative evaluations of adrenal function were conducted while the patient ingested a constant metabolic diet containing 2.1 mEq of sodium per kg of body weight each day. The 24-hour urine specimens were collected in 10N sulfuric acid for measuring catecholamine excretion[7] and in

Refer to: Kirby BD, Ham J, Fairley HB, et al: Normotensive pheochromocytoma: Pharmacologic, paraneoplastic and anesthetic considerations, West J Med 1983 Aug; 139:221-225.

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glacial acetic acid for determining aldosterone excretion.[8] Specimens for measuring plasma renin activity were collected after overnight recumbency and after two hours of upright activity.[8]

Blood pressure and heart rate were measured every two to four hours after the patient had been recumbent for ten minutes and after standing for one minute. The response of blood pressure and heart rate to administration of glucagon, phentolamine, norepinephrine and angiotensin II was also evaluated. These studies were done after the patient had been recumbent for at least 30 minutes and after blood pressure and heart rate had stabilized. Glucagon, 1 mg, was administered intravenously as a rapid infusion. Phentolamine was administered intravenously in 1-, 2- and 5-mg increments. Norepinephrine was infused at increasing rates up to 20 μg a minute in the patient and in seven normal control subjects. Angiotensin II amide was infused at increasing rates until the diastolic blood pressure had risen by 20 mm of mercury from control values. The protocols were approved by the Committee on Human Research of the University of California, San Francisco, and the patient and control subjects gave informed consent.

Preoperative Evaluation

Urinary levels of dopamine, norepinephrine, total metanephrines and vanillylmandelic acid were consistently in excess of the range of values in normal subjects (Table 1). Urinary epinephrine was not detected. Urinary aldosterone excretion was 8.0 μg per 24 hours (normal 5 to 20). Plasma renin activity was 3.3 ng per ml an hour when the patient was recumbent (normal 0.4 to 2.9) and 8.9 after two hours of upright position (normal 1.1 to 13.5).

Average values of recumbent and upright blood pressures recorded frequently over a four-day period (N=32) were 122±2/73±2 and 101±2/66±2 mm of mercury, respectively. The highest value observed during this interval was 134/90 mm of mercury. Average values of recumbent and upright heart rates were 71±1 and 100±3 beats per minute, respectively.

In response to infusion of glucagon, the blood pressure rose from a baseline level of 120/80 to a maximum value of 180/120 mm of mercury five minutes after infusion (Figure 1). At that time, the patient experienced a feeling of warmth and complained of palpitations. His heart rate during the test slowed from 92 to 78 beats per minute. Norepinephrine and epinephrine levels in urine collected for two hours after glucagon administration were 150 and 1 μg, respectively.

In a response to the 1-mg dose of phentolamine, the blood pressure fell transiently from 120/62 to 100/50 mm of mercury and the heart rate increased from 84 to 96 beats per minute. In response to the 2-mg dose, the blood pressure fell from 120/66 to 106/50 mm of mercury and the heart rate increased from 84 to 100 beats per minute. After the 5-mg dose, the blood pressure fell from 120/66 to 110/40 mm of mercury and the heart rate increased from 80 to 104 beats per minute; this response lasted for eight minutes.

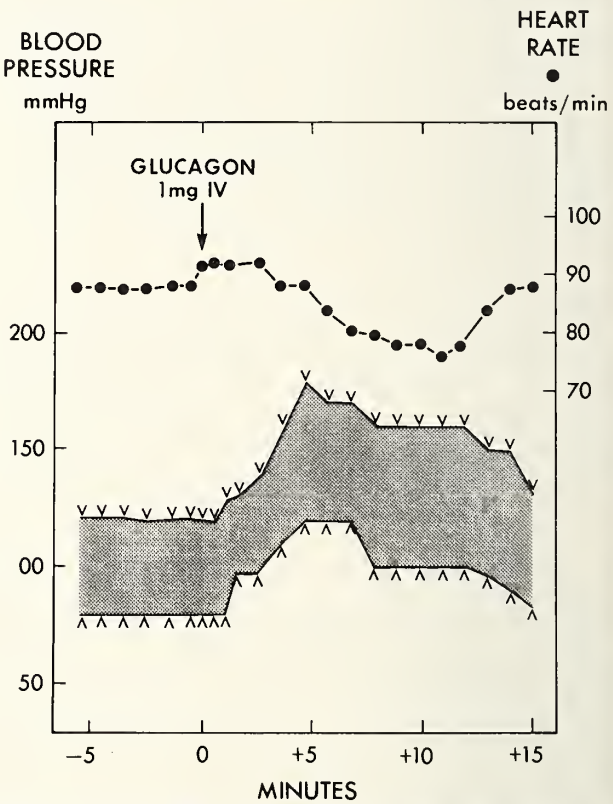

Figure 1.—Response of blood pressure and heart rate to infusion of glucagon.

TABLE 1.—*Preoperative and Postoperative Laboratory Data*

Date	Blood					Urine					
	Hematocrit Percent	ESR mm/h	Alkaline Phosphatase IU/liter	Albumin Grams/dl	Globulin Grams/dl	Norepinephrine μg/24h	Epinephrine μg/24h	Dopamine μg/24h	Metanephrine μg/24h	VMA mg/24h
Sep to Nov, 1975	30.2	122	445	3.2	4.1	...	...	...	...	...
May to Jun, 1976	29.5	59	800	2.7	5.6	985-1,005	0	1,720	1.9-3.3	15.8-18.9
Jun 18, 1976				Resection of Pheochromocytoma						
Jul 21, 1976	34.9	18	75	4.1	3.2	118	1	277	...	4.3
Jan, 1979	43.9	...	58	3.6	2.9	72-103 (n=3)	1-8 (n=3)	...	0.3-0.5 (n=3)	4.7- 6.4 (n=3)
Normal values	39.0-53.0	<15	20-80	4.3-5.6	1.9-3.4	0-105	0-25	50-350	<1.3	1.8- 9.0

ESR=erythrocyte sedimentation rate; VMA=vanillylmandelic acid.

The patient had a generalized sensation of warmth after administration of the largest dose.

In response to infusion of norepinephrine at a dose of 20 μg a minute, the systolic blood pressure rose by 27 and the diastolic blood pressure by 10 mm of mercury. The heart rate decreased by 16 beats per minute. The rises in blood pressure noted in seven normal subjects who were matched for age and studied under similar conditions were recorded as follows: systolic, 38±2 mm of mercury (range 32 to 48), and diastolic, 23±3 mm of mercury (range 10 to 35). The heart rate in normal subjects slowed by 11±3 beats per minute (range 2 to 28).

The infusion rate of angiotensin II required to raise the diastolic blood pressure by 20 mm of mercury was 13.6 ng per kg a minute. Normal subjects require an average of 7.4 ng per kg of body weight per minute (range 6.0 to 11.4) to achieve the same rise in blood pressure.[9]

Preoperative and Intraoperative Management

The results of the biochemical measurements and pharmacologic tests were considered indicative of a diagnosis of pheochromocytoma. In anticipation of surgical intervention, treatment with phenoxybenzamine hydrochloride, 10 mg daily by mouth, was begun. On the following day, orthostatic hypotension (blood pressure 70/40 mm of mercury on standing) and chest pain developed and the medication was discontinued. Blood volume measurements showed that the erythrocyte volume was decreased (14.3 ml per kg of body weight, normal 22 to 28), the plasma volume was increased (51.7 ml per kg, normal 35 to 43) and the total blood volume was normal (66.0 ml per kg, normal 57 to 71). Two units of whole blood and one unit of packed erythrocytes were administered preoperatively.

On the day of the surgical procedure, June 18, 1976, morphine sulfate, 10 mg, and scopolamine methylbromide, 0.5 mg, were administered intramuscularly for preanesthetic sedation. The initial blood pressure taken in the operating room was 140/70 mm of mercury and heart rate was 45 beats per minute. Intravenous administration of atropine sulfate, 0.4 mg, resulted in increases in the heart rate to 90 beats per minute and the blood pressure to 210/140 mm of mercury and in a ventricular bigeminal rhythm. Administration of phentolamine, 1 mg given intravenously, reduced the blood pressure to 130/90 mm of mercury and the heart rate to 70 beats per minute.

Hemodynamic determinations were made before inducing anesthesia, during the operation and in the recovery room. Systemic vascular resistance preoperatively was 10 mm of mercury per liter per minute and rose to a maximum of 31.7 mm of mercury per liter per minute during tumor manipulation (normal range, 12 to 20 mm of mercury per liter per minute). The intraoperative course was characterized by pronounced lability of blood pressure and heart rate and the occurrence of cardiac arrhythmias. Hypertension, which occurred primarily during manipulation of the tumor, was managed successfully with 1 to 2 mg of intravenous bolus injections of phentolamine. Episodes of nodal and ventricular tachycardia resolved spontaneously when the blood pressure fell. Transient hypotension (100/50 mm of mercury) followed removal of the tumor. This was corrected by fluid replacement of 2,000 ml of whole blood and 3,000 ml of crystalloid intraoperatively.

Operative Findings and Subsequent Course

A well-encapsulated left adrenal tumor weighing 90 grams was removed completely. The gallbladder, common bile ducts and right adrenal gland appeared normal. A splenectomy was done and a liver biopsy specimen was taken. The adrenal tumor was composed of nests of uniform-appearing cells with bland oval nuclei and diffusely scattered, fine brown granules. No evidence of malignancy was found. The liver biopsy specimen showed pericholangitis and hemosiderosis.

No complications occurred in the immediate postoperative period; the patient became asymptomatic, afebrile and gained weight eventually to his normal weight. In the seven years since the operation, the patient has remained free of symptoms. The mean recumbent and upright blood pressures measured during a five-day period of in-hospital observations in 1979 were 111±2/69±2 and 105±2/71±2 mm of mercury, respectively (N=13), and heart rates were 58±1 and 78±4 beats per minute, respectively. All laboratory abnormalities resolved promptly (Table 1).

Discussion

The subjective symptoms of palpitations, sweats, headache, postexertional emesis and weight loss reported by the patient were quite consistent with the diagnosis of pheochromocytoma. The objective findings, however, of a normotensive patient presenting with a fever of unknown origin, anemia, thrombocytosis, elevated erythrocyte sedimentation rate and serum alkaline phosphatase level, prolonged prothrombin time and reversal of the albumin-globulin ratio were unusual enough that the diagnosis was not immediately established. Laboratory abnormalities unrelated to catecholamine excess are distinctly unusual in patients who have nonmetastatic pheochromocytoma. Indeed, several of these paraneoplastic findings are previously undescribed in association with pheochromocytoma.

In a review of 118 patients with pheochromocytoma published in 1950, Smithwick and co-workers[10] reported "unexplained elevations of body temperature (1°F or more)" in more than 70% of patients. The low-grade fevers occurred in the absence of paroxysmal symptoms and appeared to be distinct from the extreme temperature elevations that occurred during paroxysmal attacks. Smithwick and colleagues urged that unexplained temperature elevations should "lead one to suspect the diagnosis of pheochromocytoma." Nonetheless, in the subsequent 30 years standard texts and contemporary reports have usually emphasized hyperthermia in association with catecholamine storm,[11] and

presentation with fever of unknown origin has been forgotten. In our patient, daily fevers were noted during the six-week period of preoperative evaluation. Indeed, the pheochromocytoma was discovered in the course of a systematic evaluation of the fever of unknown origin; the diagnostic mesenteric arteriogram was to have been the final study before laparotomy for presumed empyema of the gallbladder.

Anemia, thrombocytosis and extreme elevation of the erythrocyte sedimentation rate are nonspecific hematologic abnormalities typically associated with tumors, including hypernephroma. Erythrocytosis, attributed to tumor production of erythropoietin, has previously been the only hematologic abnormality described regularly for patients with nonmetastatic pheochromocytoma.

In 1961, Stauffer[12] described five cases of patients with hypernephroma who had an associated hepatopathy characterized by an elevated hepatic alkaline phosphatase level, a prolonged prothrombin time and reversal of the albumin-globulin ratio. These findings were unassociated with histologic abnormalities observed in the liver biopsy specimen, and all abnormalities resolved after removal of the tumor. Subsequent experience has corroborated Stauffer's observations.[13] In our patient, a reversible hepatopathy identical to that described by Stauffer and not previously described in association with pheochromocytoma was documented. Recognition of this as a paraneoplastic syndrome rather than a consequence of metastatic disease is clearly important from both a diagnostic and a therapeutic standpoint.

Norepinephrine is the principal catecholamine secreted by most pheochromocytomas. Hence hypertension, sustained or intermittent, is present in most patients who have this disorder. In some patients, however, hypertension is not present; its absence has been attributed to predominant epinephrine secretion,[1,2,6] myocardial failure due to catecholamine-induced cardiomyopathy, tissue receptor tolerance,[5] inactivation of catecholamines within the tumor[4] and predominant or coincident secretion of dopa and dopamine.[3]

Epinephrine is the predominant catecholamine secreted in a few patients. The clinical presentation of an epinephrine-secreting pheochromocytoma is often characterized by hypotension and ventricular and supraventricular tachyarrhythmias and may mimic septicemia, intra-abdominal catastrophe, pulmonary embolism or myocardial infarction. The β-adrenergic effects of epinephrine on the peripheral vasculature and myocardium may explain these findings. Epinephrine secretion was not increased in our patient and therefore is not an explanation for the lack of hypertension.

Tolerance of tissue receptors to catecholamines was postulated as an explanation for normotension in a patient with pheochromocytoma despite high levels of circulating norepinephrine.[5] In an in vitro frog erythrocyte model, a decrease of up to 70% of β-adrenergic receptors was found after chronic stimulation with catecholamines.[14] A decrease in the number of β-adrenergic receptors has also been shown in vivo in rats that have pheochromocytoma.[15] The response to infusion of norepinephrine in our patient was comparable to values in control subjects indicating that tissue receptor tolerance to an extent that would alter responses to circulating catecholamines was not present and could not be invoked as the probable cause for the absence of hypertension.

Excess secretion of dopamine and dopa has also been postulated as an explanation for normotension in some patients who have pheochromocytoma.[3,16-19] Both substances have vasoactive properties that can explain the absence of hypertension despite elevated circulating levels of norepinephrine. Administration of dopa decreases recumbent and standing blood pressures in humans. The mechanism appears to be mediated through the central nervous system.[16] In addition, dopa is converted to the catecholamine dopamine, which also has direct hemodynamic effects. The hypotensive action of dopamine may result from direct vasodilatation of mesenteric and renal vasculature, from competition between dopamine—a less potent α-adrenergic stimulator—and norepinephrine for α-adrenergic receptors or from a urinary loss of sodium (or all three).[14-16] A balance between the hypertensive effects of norepinephrine and the hypotensive effects of dopamine has been suggested as the explanation for the absence of hypertension noted in other catecholamine-secreting tumors such as neuroblastoma, sympathoblastoma and ganglioneuroma.[19] Dopamine modulation of the hypertensive effects of norepinephrine may be the best explanation for the absence of hypertension in our patient, as well as in previously reported cases.[3]

The intraoperative mortality in patients with unsuspected pheochromocytoma may approach 50%.[20] As a result, extreme care in the preoperative preparation and the intraoperative management is taken in a patient with known pheochromocytoma. In hypertensive patients, preoperative preparation usually consists of α- and β-adrenergic blockade with phenoxybenzamine and propranolol for several weeks before a surgical procedure. In normotensive patients, preoperative blockade is more controversial.[6,21] For example, our patient became symptomatic during phenoxybenzamine therapy. In retrospect, this response to α-adrenergic blockade as well as the intraoperative hemodynamic instability may have been prevented or attenuated by more aggressive preoperative blood transfusion. Despite the finding that most patients have normal blood volumes when measured preoperatively, most also show relative hypovolemia that may be prevented by overtransfusion.[21]

The patient arrived in the operating room with pronounced sinus bradycardia and a normal blood pressure. The cause of the bradycardia was unclear, but it was elected to use atropine because of the concern that a less favorable rhythm might occur with induction of anesthesia. The response to atropine was an increase in heart rate, ventricular bigeminy and hypertension that required treatment with phentolamine. Such a response has been described after atropine premedication

in patients who have received preoperative α-adrenergic blockade.[20]

The intraoperative responses in our patient were similar to those of hypertensive patients with pheochromocytoma. Some lability of blood pressure and heart rate was seen, especially upon manipulation of the tumor, and treated with phentolamine. Several episodes of nodal and ventricular tachycardia in association with the hypertensive responses to manipulation of the tumor resolved after control of the blood pressure. Hemodynamic monitoring showed that, before anesthesia, systemic vascular resistance was below the normal range, cardiac index was increased and blood pressure was normal. These findings are consistent with the hypothesis that the patient had a hormonal milieu blunting the usual α-adrenergic response to norepinephrine. Nevertheless, during manipulation of the tumor, both blood pressure and vascular resistance increased considerably, suggesting that under these circumstances the catecholamine balance changed to an α-adrenergic predominance. Subsequent to clamping the venous drainage from the tumor, vascular resistance and blood pressure fell.

The spectrum of the presentation of pheochromocytoma continues to expand. Hypertension may be absent despite excess norepinephrine secretion. Fever of unknown origin, anemia, extreme elevation of the erythrocyte sedimentation rate and hepatopathy may be added to the spectrum of paraneoplastic syndromes caused by this neoplasm.

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Remembrance of Things Past: Aortobronchial Fistula 15 Years After Thoracic Aortic Homograft

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THE EVOLUTION of prosthetic vascular grafts has included the development of diverse materials, starting with the Vinyon-N fabric of Blakemore and Voorhees and progressing to the use of Dacron, expanded Teflon, bovine carotid artery and preserved human umbilical vein. In the 1950s intense interest attended the use of human cadaver arteries, preserved in various ways, for vascular substitutes. These arterial homografts were readily available and technically easy to handle, had a reasonable patency rate in the short term and were used commonly in many different clinical circumstances. The first replacements of the aorta for aneurysm and occlusive disease used these conduits. About 1956, however, it became clear that the homograft preservation process and constant pulsatile arterial pressure led inevitably to a loss of structural integrity and graft degeneration.[1,2] Aneurysm formation or fibrosis leading to graft rupture or occlusion caused the use of these grafts to be abandoned, a move hastened by the parallel development of acceptable polyester grafts. Arterial homografts were still available in many hospital operating rooms until the mid-1960s but subsequently have almost completely disappeared from use. Homograft tissue is now rarely used in cardiovascular surgical procedures, except for cardiac valve replacement using tissue-bearing prostheses.[3,4]

We describe the case of a patient who underwent aortic repair using an arterial homograft, in whom lethal complications developed 15 years later because of this graft. With this report we hope to alert clinicians to the potentially catastrophic complications that may result from these grafts and we propose diagnostic maneuvers that may forestall them.

Report of a Case

In 1965 a 20-year-old man sustained a blunt thoracic deceleration injury in an auto accident. He underwent

Refer to: Oldham KT, Johansen K, Winterscheid L, et al: Remembrance of things past: Aortobronchial fistula 15 years after thoracic aortic homograft. West J Med 1983 Aug; 139:225-228.

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placement of a Teflon interposition graft to repair a tear of the descending thoracic aorta. This procedure was complicated by a graft infection that required replacement of the Teflon graft with an aortic homograft. Subsequently the patient did well.

Fifteen years later the patient, now 36 years old, was seen by his private physician because of worsening of chronic asthma associated with atopy. He had no evidence of infection and no history of hemoptysis, but he had recently increased his cigarette consumption. Roentgenograms of the chest confirmed the previously noted findings of chronic left upper lobe fibrosis and aortic calcification (Figure 1). Oral aminophylline therapy was begun, resulting in lessened wheezing and improved pulmonary function, but the patient had ongoing malaise. Three weeks later he coughed up a large amount of blood and shortly thereafter had respiratory arrest. Seattle Medic-I[5] paramedic personnel found the patient unresponsive and apneic and with a pulse rate of 40. An orotracheal tube was inserted and he was given 100% oxygen; large-bore intravenous lines were placed and the patient was transported to the emergency ward of Harborview Medical Center under continuous cardiopulmonary resuscitation.

On arrival, the patient was arousable. He had a pulse of 115 per minute and a systolic blood pressure of 100 torr (mm of mercury). Blood was noted in the endotracheal tube, and no breath sounds were heard over the left upper thorax. Hoarse rhonchi were audible throughout the chest. A chest roentgenogram showed a heavily calcified aortic arch and descending thoracic aorta; the left upper lung field was completely opacified. Arterial blood gas determinations done while the patient was receiving 100% oxygen showed a pH of 7.02, a partial carbon dioxide pressure (P_{CO_2}) of 69 and a partial oxygen pressure (P_{O_2}) of 217 mm of mercury. Hematocrit was 35%.

The patient was taken directly to the operating room with the intent of doing bronchoscopy and thoracotomy, with a presumptive diagnosis of a ruptured pseudoaneurysm of the descending thoracic aorta. On arrival in the operating room he again had massive hemoptysis; his endotracheal tube was cleared, then advanced into the right mainstem bronchus. Despite these maneuvers, the patient had respiratory, followed by cardiac, arrest, and cardiopulmonary resuscitation was reinstituted. An emergency left anterior thoracotomy was done. Entry into the chest was remarkably difficult because of extensive fibrotic adhesions and massive bleeding. He was found to have an extremely brittle, calcified pseudoaneurysm of the aortic arch from the left subclavian orifice to the midthoracic aorta; this had ruptured into the left upper lobe of the lung. The patient died before the hemorrhage was controlled.

Postmortem examination showed dense periaortic adhesions in the left thorax; multiple pseudoaneurysmal dilations of a patent, fibrotic aortic homograft conduit just distal to the left subclavian artery were noted. One of these aneurysms had ruptured into the left upper lobe bronchus (Figure 2).

Comments

The occasional but disastrous development of an aortoenteric fistula, pseudoaneurysm or prosthetic vas-

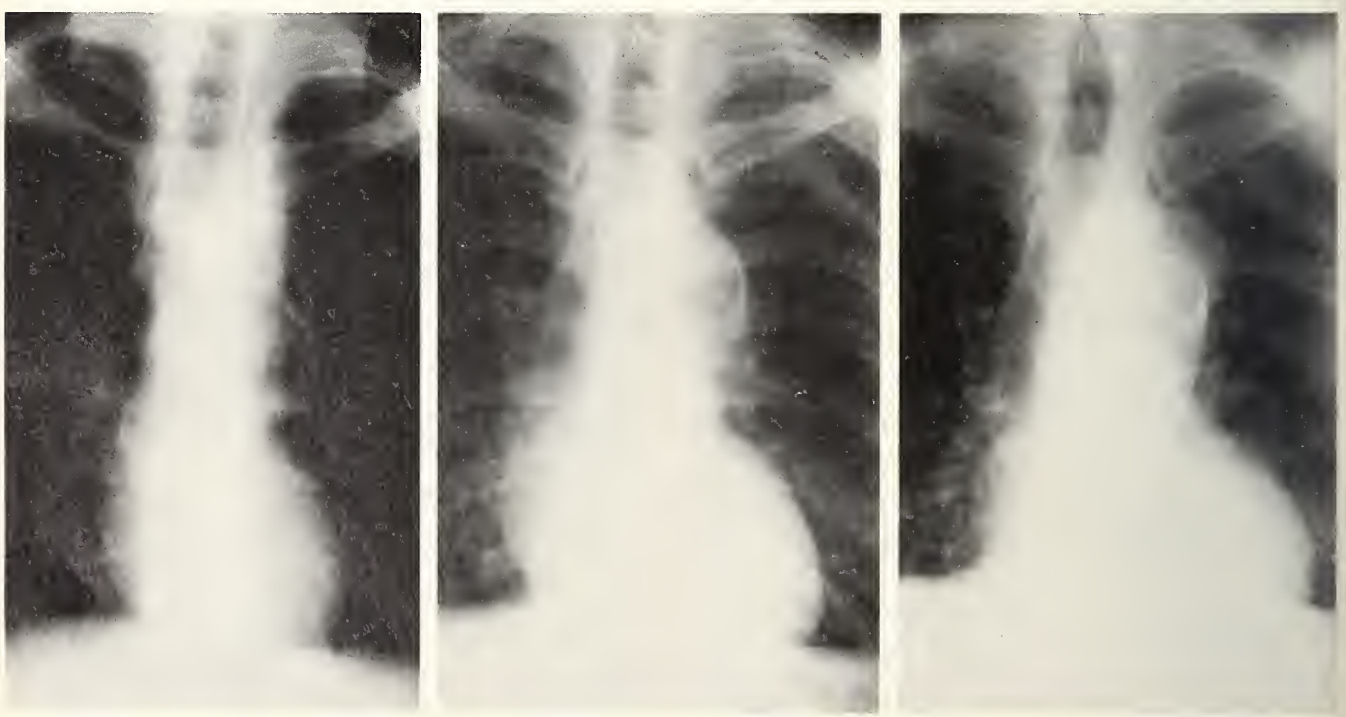

Figure 1.—Chest roentgenograms five months **(left)**, ten years **(center)** and 15 years **(right)** after thoracic aortic interpositional graft with cadaver arterial homograft. Note development of aortic homograft calcification.

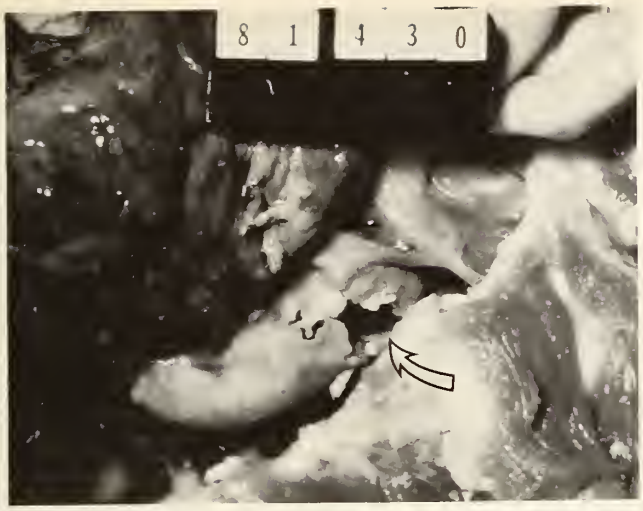

Figure 2.—Photograph at postmortem examination showing ruptured pseudoaneurysm of thoracic aortic arterial homograft **(arrow).** The pseudoaneurysm ruptured into the left upper lobe of the lung **(upper left corner of photograph).** (Photograph courtesy of King County Medical Examiner's Office.)

cular graft infection reminds cardiovascular surgeons that the implantation of foreign materials into the arterial tree has an ongoing and cumulative risk of complication. The Proustian title of our report underscores the fact that such complications may be significantly delayed—in this case for a decade and a half.

The use of homograft tissue for vascular replacement has definite appeal, for such conduits are readily available and material qualities such as elasticity, compliance and strength would seem to be relatively advantageous. Unfortunately, the use of fresh cadaver material for vessel or valve grafts generally violates the "self/not-self" immune barrier,[6] and such material is eventually rejected by the host. Similarly, though various preservation techniques—such as freeze-drying,[7] immersion in ethylene oxide[8] or β-propiolactone,[9] or electron irradiation,[7]—appear to blunt or ameliorate the antigenic stimulus, the benefits of such methods are apparently offset by the production of structural damage to the graft at the cellular level, and these tissues thus generally undergo necrotic or fibrotic degeneration. Initially, arterial homografts generated enthusiasm because of excellent short-term results when used for arterial bypass or replacement.[10-12] Within a year or two after implantation, however, these grafts developed unacceptably high rates—greater than 50%—of thrombosis, aneurysm formation or infection[1,2,13-15] and their use was rapidly eschewed in favor of innovations in plastic grafts. Homograft tissue is now rarely used in cardiovascular operations—occasionally for conduits in the Fontan procedure and for cardiac valves,[3,4]—where it has been associated with modest short- and medium-term results.

Massive hemoptysis, a common occurrence during the tuberculosis era, is now seen much less often and usually arises from blunt or penetrating chest trauma or malignancy involving the bronchial arterial circulation.[16] Hallmarks of management include simultaneous resuscitation and diagnosis, the latter by means of rigid bronchoscopy, chest roentgenography and pulmonary and bronchial arteriography. Massive persistent bleeding may be controlled immediately by intubation of the contralateral (normal) bronchus by single- or double-lumen endotracheal tubes or Fogarty catheters,[17] by angiographic embolization[18] or by emergency thoracotomy and lobectomy or pneumonectomy.[19] The death rate remains high.

In our patient a lethal outcome was virtually preordained because the diagnosis was not suspected until his homograft pseudoaneurysm ruptured into the bronchial tree. A thoracotomy to resuscitate the moribund patient met impenetrable adhesions and massive bleeding in the left upper hemithorax. Balloon tamponade of the thoracic aorta[20] proximal to this point via the axillary artery might have been considered but would have risked carotid occlusion and stroke. Had the presence of incipient graft rupture been anticipated, or even considered, when the patient presented three weeks earlier with worsening of his asthma, elective thoracic aortic replacement (probably with en bloc left upper pulmonary lobectomy) using adjunctive cardiopulmonary bypass might have offered him the chance of long-term survival.

The vast majority of patients who underwent placement of preserved homograft arteries for bypass or interposition in the 1950s were elderly persons who had arteriosclerosis, and it is unlikely that many have survived the subsequent quarter century. A number of infants and children, however, underwent homograft arterial interposition grafting for various congenital cardiovascular defects during that time. Robert Gross, MD, inserted homograft aortic conduits in almost 100 young patients who had aortic coarctation, for example (reported in conversation, 1981). These persons have now reached young adulthood. The literature shows, with few exceptions,[14,15] little long-term follow-up of these or other young patients who had implantation of these cadaver arterial grafts. We suspect that, as in our case, the obvious but chronic chest roentgenographic abnormalities, coupled with a lack of appreciation of the well-documented but obscure natural history of arterial homografts, may prevent recognition of the lethal potential of these grafts.

Our case's fatal outcome, combined with the known cumulative incidence of complications of these grafts, leads us to suggest that all patients, asymptomatic or not, who have had placement of such homograft vascular conduits at any time in the past should be considered for elective graft replacement. At the least, such persons should be serially evaluated by computed tomographic scan or ultrasound studies, if not arteriography, to delineate possible evidence of graft degeneration—dilatation, aneurysm formation, extensive calcification and so on. Such findings might lead to a decision favoring elective graft excision and replacement. Thus, we are in agreement with Meade and col-

leagues, who closed a 1966 report on the long-term fate of arterial homografts by commenting: "Confirmed follow-up of all . . . cases is essential since graft failure may occur at any time regardless of how long the graft has been placed."[13(p399)]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

The Legal Requirements of Medical Practice

To the Editor: Traditionally, medicine was a biological science. For two decades the health field has been infiltrated by the legal establishment changing the nature of healing art into a legal act. The legal interest in medicine was attracted by the still inaccurate knowledge of life itself and the margin of error of all human acts. This change forced an unprecedented personal accountability on health practitioners and generated millions of dollars of income for attorneys. We would expect that accountability and liability would be defined by law—for example, who can prescribe narcotics or who can sign a death certificate. The liability crisis has no such characteristics of an orderly legal process. It was shaped in courtrooms, by judges and attorneys without specific statutes, assuring princely profits for the "officers of the court."

Organized medicine should strive for an orderly constitutional process where the perimeters of accountability and liability are stated by law: when to use fetal monitor, when to call for genetic counseling or disconnect the life support system. Do we have to document that Sunday afternoon call from a patient? Is clinical judgment dead and must every observation and complaint be documented by objective tests? Are the recommendations of the manufacturer in the package insert binding? If they are, they have the strength of law—or have they? The nebulous description of "informed consent" should be formalized, black and white. The popular term "standard of care" should be elevated from generalities to definition. Only a fraction of medical practices are uniform in most communities. Most practices are divergent due to schooling, experience or conviction. The views of a physician after 30 years of practice are different from those of a newcomer. If a "standard of care" is binding, it should be known to every practitioner. Legal accountability should be determined by law before it is enforced. Guilt and accountability should not be created in a retrograde manner after the fact just because it is profitable for the attorneys.

There are numerous aspects of diagnosis and treatment that represent personal liability for the physician without statutory definition. This is a giant gray area with unlimited opportunities for claims. The disposition of a case is then determined by aggressiveness and cunning, by rhetorical skill, emotional tricks and courtroom theatrics. The armamentarium of attorneys is immense: exaggeration, misrepresentation of facts, embarrassment, exhaustion and intimidation of defendants, witnesses and opposing lawyers, emotional manipulation of judge, jury, audience and media. Justice will be determined by the most successful manipulators of emotions and suggestibility. Our system is ruled by men and not by law.

If the government can enforce accountability, it should be the government's responsibility to state unequivocally by law who is accountable for what. It should issue an authoritative document: "The Legal Requirements of Medical Practice." Public policy as expressed by laws should be framed by elected representatives, not by the judicial branch. This should be included in the curriculum of medical schools. It should be part of licensing examinations. It should be published and issued to every practitioner. Then and only then should liability be enforced. I do not want to minimize the difficulties of compiling such a document but we have few alternatives left to resolve the liability crisis. Organized medicine should strive for this goal within the framework of a broader judicial reform.

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Beware of Phenolic Antioxidants (BHT and BHA)

To the Editor: During a recent plane flight I came across an article in an airline magazine (*PSA Magazine,* April 1983, p 73) that reports an interview with Durk Pearson and Sandy Shaw, authors of the best-seller *Life Extension—A Practical Scientific Approach.* The article provides a platform for Pearson and Shaw to "give some advice on keeping hair on your head, memories in your brain and the spring in your step as you dance with Father Time." In the interview, as a counterattack to *disordered nutrition* (apparently "excessive fat in the diet, particularly polyunsaturated fat") which may be involved in age-related problems, Pearson recommends *inter alia* supplements of "BHT and BHA, common antioxidant food preservatives." Later, in discussing the assertion that BHT has been very effective in eliminating genital herpes outbreaks and preventing the virus from being communicated, Pearson is

stated to "recommend taking a daily dose of two grams of BHT just before bedtime indefinitely because the BHT attacks the virus itself, preventing it from reappearing or being transmitted. . . . BHT has also been found to be a preventative agent against certain types of cancer." These views of Shaw and Pearson were also expounded in a *Wall Street Journal* article about them (May 2, 1983, p 1).

Whatever the actual merits of BHT (and BHA) might be in combatting the awesome triad of senescence, genital herpes and cancer, I wish to bring to the attention of physicians and health personnel that many years ago Denz and Llaurado[1] reported dramatic, deleterious effects of 2:6-di-*tert.*-butyl-4-methylphenol (BHT) and butylated hydroxyanisole (BHA), which is a mixture of two isomers, 85% being 2-*tert.*-butyl-4-methoxyphenol and 15% 3-*tert.*-butyl-4-methoxyphenol. These phenolic antioxidants are used in small concentrations for the stabilization of edible fats.

In well-controlled experimental studies Dr F. A. Denz and I found[1] that a series of daily doses of 1 gram of BHT (or BHA) given to rabbits by stomach tube led to muscular weakness, inanition and death. The biochemical and histological studies included electrolyte (Na^+ and K^+), extraceliular fluid and corticoadrenal data. The organs most affected were skeletal muscles, kidneys and adrenal glands. We indicated that the possible cause of death was potassium depletion. At the time that we published our results, we believed that the relatively low levels of BHT and BHA used as antirancids for food preservation were not harmful to humans. In spite of the appearance in recent years of faddist groups vociferating against preservatives added to food, I still believe (Dr Denz is now deceased) that the above statement is true and personally felt for some time that I should not "reissue" our data because they could unjustifiably alarm consumers or might be misconstrued as a publicity seeking device on my part.

However, after reading that daily doses of 2 grams of BHT are recommended indefinitely "to attack" the genital herpes virus, I feel, in good conscience, compelled to draw attention to the toxic effects associated with the administration of BHT and BHA that have been experimentally demonstrated by us on rabbits. Daily doses of 1 gram given to rabbits were lethal in about two weeks. In terms of concentration of drug per kg of animal mass, the recommended human dosc of 2 grams a day is simply *one order of magnitude* below thc lethal dose. Obviously, smaller doses, if not lethal, must produce pathological effects.

I havc not read *Life Extension,* but from the information gleaned from the two articles I have mentioned, I feel impelled to make a strong effort to prevent administration of chemicals that have been shown to havc devastating effects in well-documented expcrimental studies. I believe physicians and health authorities should be familiar with the probable consequences of prolonged large doses of these phenolic antioxidants and forbid their use except as fat stabilizers for food. These agents may *do in* not only the virus itself, but indeed the host as well.

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Lessons From the 4077th M*A*S*H

To the Editor: After a quick search through the *Index Medicus,* I realized not much has been written about M*A*S*H. It seems inappropriate that the passing of a television show that has shaped America's (and probably the world's) view of physicians in the military should occur without note in the medical literature. Eleven years and 250 shows have truly changed our impression of doctors in wartime, not only career military but drafted doctors and even psychiatrists.

We noted in the movie M*A*S*H that wartime doctors might be "different" but we actually learned it while tuning into CBS once a week for all those years. It was a show that grew with us. In the wake of the Vietnam War, we and it changed, both being affected by the changing American culture. We watched Hawkeye go from womanizer to feminist, Margaret Houlihan from "Hot Lips" to a constructive partner in a health care team. We also saw Frank Burns' fanatical patriotism stinted, and Radar's naiveté squashed. Throughout all this, we tried to convince ourselves it was the witty writing, superb acting, flawless delivery and cast teamwork that made us tune in. We didn't understand that a culture was undergoing a metamorphosis around us, both in medicine and throughout society and M*A*S*H. Character changes were symbolizing that change. Actually, the 20-year time difference "removed" it from the present and made it safe to watch. Little did we realize it was the American soul up there on the screen.

While using the Korean War in the 1950s as a metaphor, the show catalogued the changes of the 11 years it was on television: sexual frankness, antiwar stirrings, feminism and so forth—in short, the lost innocence of the children of the 1970s. Trapped in the insanity of a wartime surgical "hospital" based in tents, the medical personnel of the 4077th tried to make sense of the inhumane conditions, irony and uncivilizing effect of war. We watched weekly. We empathized. We identified.

When the Vietnam War was over and the culture shifted slowly into the "me decade," we noticed the cast internalize; plots emphasizing interpersonal relationships and personal fulfillment began to be aired. Nuances of relationships were explored. They changed. We changed. A whole generation of Americans changed.

Where do we go from here? M*A*S*H is over; we have lost a friend. Perhaps something else can fill the self-reflective void we now might have. Perhaps in the 11 years since its start, we have learned how to do that self-reflection ourselves.

To the 4077th M*A*S*H: Goodbye, farewell, amen.

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Hypervitaminosis A, Hypercalcemia and Hemodialysis

To the Editor: I wish to clarify two statements, and to give additional information, concerning the recent report by Baxi and Dailey on "Hypervitaminosis A: A Cause of Hypercalcemia."[1]

The authors state, "Hypercalcemia has been reported only rarely [in relation to hypervitaminosis A] and approximately seven patients have been described previously." However, at least 6 additional cases (a total of 13 or more) were linked to vitamin A toxicity by 1978 (examples are cited in references[2-4]). Hypercalcemia is actually reported in roughly a quarter to a third of all cases, at least in adolescents and adults, and it could be considered a fairly common symptom. I agree with Baxi and Dailey, however, that hypervitaminosis A may be too rarely *considered* as a cause of hypercalcemia, and their report is valuable to emphasize this point.

The authors' statement that hypervitaminosis A "has led to fatal portal hypertension on occasion. . . ." is not well founded. No fatalities are mentioned in the authors' references for this statement. In fact, in my study of the literature,[5] I have found *only one death* ever attributed to vitamin A—an English PhD chemist whose cause of death was stated to be liver cirrhosis, without mention of portal hypertension.[6] Despite illness and medical warnings, he took supplements of more than a million IU daily for long periods. Polar bear liver is well known to sometimes cause brief, acute symptoms, but apparently without reported fatalities.[5]

It is not clear how vitamin A has acquired its lethal reputation. Other nutrients with lesser reputations for toxicity have caused far more fatalities; for example, there have been perhaps a score of deaths in the United States from vitamin D, and hundreds from iron supplements ingested by children.

An additional valuable report concerns patients undergoing hemodialysis. They seem to be unusually sensitive to vitamin A supplements and prone to hypercalcemia which abates when supplements are withdrawn.[7] This report, like that of Baxi and Dailey, presents information which can help physicians prevent and correctly diagnose vitamin A toxicity.

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Drs Dailey and Baxi Reply

To the Editor: We wish to thank Dr Davis for his comments and interest in our case report. We appreciate his pointing out additional instances of reported hypercalcemia with vitamin A intoxication not cited in our references. The frequency of hypercalcemia is difficult to state with certainty; this clearly does underscore the need to consider it as a cause of readily reversible hypercalcemia.

Dr Davis is also correct in stating that death did not occur in the instance of cirrhosis and portal hypertension cited in our references. This was cited principally as the best histologic verification of this finding. Reference 6 in Dr Davis' letter is perhaps the best documented death in humans. Certainly, a variety of hepatic lesions have been reported in adults as well as children. While documented deaths have also occurred in laboratory animals, the doses and duration of therapy necessary to produce the lesions remain open to question.

The purpose of our case report was certainly not to denigrate the importance of vitamin A and other retinols in human nutrition and its potential importance in prevention of other serious illnesses. However, there remains no clear documentation of benefit in prescribing amounts of vitamin A far in excess of the current recommended daily allowances. We continue to feel that the use of pharmacologic doses of potentially toxic substances, especially fat soluble vitamins, should be more carefully controlled and available through prescription only.

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Topics in Primary Care Medicine

Thyroid Hormone Replacement

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Hypothyroidism is one of the most common endocrine diseases seen by general internists. Questions frequently arise about the appropriate thyroid hormone preparation and dosage and how best to monitor these patients. In this article we will address these questions and make recommendations in light of a number of recently published observations.

Most authorities now believe that levothyroxine sodium (L-thyroxine) is the drug of choice for thyroid hormone replacement or suppressive therapy. In spite of this, a significant proportion of patients continue to receive maintenance regimens of thyroid extract and several problems may occur in these patients. A number of studies have shown significant variations in total T_4 (thyroxine), T_3 (triiodothyronine) and T_4/T_3 ratio among different preparations of thyroid extract. Armour thyroid extract has consistently been shown to contain the specified amount of active hormones, whereas various generic preparations have contained from 50% to 120% of active hormone. This variation could be harmful to infants and children with hypothyroidism as well as to adults with both angina pectoris and hypothyroidism. One study of a large group of patients on a regimen of 130 to 185 mg (2 to 3 grains) of thyroid extract per day found nearly half to have elevated serum T_3 levels and normal T_4 levels. On clinical evaluation of these patients, 15% were felt to have symptoms of hyperthyroidism that resolved on treatment with levothyroxine. In addition, there is consistent postabsorptive T_3 elevation in patients receiving thyroid extract. This can be explained by rapid absorption of T_3 from the gut producing supranormal postabsorptive peaks which decline into the normal range before the next dose. Most patients apparently tolerate these wide fluctuations and there are no conclusive data on whether these transient elevations in T_3 adversely affect the cardiovascular, skeletal or nervous systems; nevertheless, it seems prudent to avoid any potential adverse effects in patients with angina pectoris or heart failure and in the elderly.

Another pitfall to be avoided with the use of thyroid extract is in the laboratory assessment of required replacement dose. High T_3 levels have already been mentioned; more confusing are the relatively low normal T_4 levels seen in patients who are otherwise clinically euthyroid. This is frequently misinterpreted by clinicians as an indication of underreplacement and could lead to unnecessary and potentially harmful increases in replacement dose. Replacement therapy with levothyroxine avoids many of the problems inherent in the use of thyroid extract. Most studies have failed to show significant differences between various preparations; although Jacobson and co-workers in 1980 reported finding a difference in bioavailability between two different brands of 10-μg levothyroxine sodium tablets.

Levothyroxine is a pure T_4 preparation that is well absorbed and has a six- to seven-day serum half-life. Conversion to T_3 occurs in the peripheral tissues. A steady state level is achieved in serum in about a month. Serum hormone levels can be drawn without adjustment for time of last dose as with thyroid extract. The currently recommended replacement dose for levothyroxine is 0.1 to 0.2 mg per day based on radioimmunoassays of thyroid-stimulating hormone (TSH) and a thyrotropin releasing hormone stimulation test. These doses are lower than previously recommended; older techniques for assessing hormone action (basal metabolic rate, cholesterol and clinical assessment) were imprecise and

Refer to: Cygan R, Rucker L: Thyroid hormone replacement (Topics in Primary Care Medicine). West J Med 1983 Aug; 139:232-233.

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were felt to overestimate requirements. Replacement doses seem to be smaller in older patients and occasionally patients require larger doses. These differences can be accounted for by variable absorption, metabolic rates and extremes of weight. Patients receiving suppressive therapy for goiter, nodules or thyroid cancer may require somewhat larger doses.

A variety of tests are now available to assess the adequacy of hormone replacement. In patients with primary hypothyroidism, the best measurement to follow is the TSH value by radioimmunoassay which should be kept in the "mid normal" range. While high serum thyroid-stimulating hormone levels are indicative of underreplacement, low or undetectable levels are not predictive of overreplacement. This measurement can be supplemented by periodic checks of the serum T_4 level, free T_4 index or the T_3 value by radioimmunoassay. Recently developed free T_4 assays may eventually be substituted for these indirect measurements of available hormone. Most patients receiving adequate replacement with levothyroxine will have a serum T_4 in the high normal range and a serum T_3 in the normal to low-normal range. Occasionally patients receiving replacement therapy will have a high T_4 level despite being clinically euthyroid with normal T_3 and thyroid-stimulating hormone levels. These cases can be followed without any dose adjustments. With pituitary or hypothalamic hypothyroidism, the T_4 and T_3 values should be monitored. The interval between tests is arbitrary. Asymptomatic compliant patients should require no more than yearly follow-up. The frequency of nonspecific symptoms compatible with underreplacement such as fatigue, depression, weakness and cold intolerance make objective evaluation a necessity before adjusting the dose.

Patients on long-term regimens of thyroid extract who are asymptomatic, have normal findings on thyroid function tests and are free of heart disease can continue to receive this therapy. If a clinician elects to switch a patient from extract to levothyroxine, the beginning dose of levothyroxine in *micrograms* should be 66% to 100% of the *milligram* dose of thyroid extract. For example, in a patient receiving 150 mg per day of extract (2½ grains), begin with 100 to 150 μg (0.1 to 0.15 mg) of levothyroxine. These recommendations are based on several crossover studies where 60 to 100 μg of thyroxine was found to be equivalent to 65 mg (one grain) of extract. Cost is not a factor since both levothyroxine and thyroid extract cost about $15 per year for equivalent doses.

Initiating replacement therapy is a common source of anxiety to internists particularly in patients with known heart disease or in the elderly. In general, replacement therapy can be begun rapidly without undue risk in adults less than 50 years old who are free of signs or symptoms of cardiovascular disease. Treatment can be initiated with 0.05 mg to 0.1 mg of levothyroxine. Follow-up examinations and thyroid-stimulating hormone studies can be done at four to six week intervals and dosages increased in 0.025 to 0.05 mg increments until the thyroid-stimulating hormone level is in the mid-normal range (3 to 5 μU per ml). As mentioned above, the average adult replacement dose is 0.1 to 0.2 mg per day. Periodic thyroid-stimulating hormone determinations can be used to confirm the adequacy of replacement. In patients over 50 years or in patients with heart disease, therapy should be initiated using 0.025 mg per day with follow-up every two to four weeks to evaluate tolerance. Dosage adjustments should be made no more than every four to eight weeks and should be guided by symptoms and thyroid-stimulating hormone levels. A recent study showed significant effects on cardiovascular, respiratory and renal function as early as the first few days after beginning replacement therapy with levothyroxine. These observations are particularly relevant to those patients with severe coronary insufficiency who require thyroid supplements. In some patients, it may be prudent to maintain a state of mild hypothyroidism in preference to risking unstable angina or a myocardial infarction. Interestingly, occasionally patients with angina will improve following thyroid replacement because of favorable changes in the myocardial function and coronary blood flow.

Another common problem is presented by the patient who has been previously placed on thyroid supplements for questionable indications. In a few of these patients, psychological dependence will preclude withdrawal and it is reasonable to simply ensure that their "replacement" dose is not excessive. In the remaining patients, the simplest method is to stop the hormone abruptly. Studies of the hypothalamic-pituitary-thyroid axis have shown that in half to two thirds of intrinsically euthyroid patients, T_4, T_3, thyroid-stimulating hormone and thyrotropin test results will be normal three to four weeks after withdrawal, and in the remainder after six weeks. Pitfalls to be aware of include a transient decrease to low normal T_4 levels in about half the patients after one to three weeks and a slight short-lived elevation in thyroid-stimulating hormone values in 25% of patients during the early withdrawal period. In the hypothyroid group, symptoms usually begin within two to three weeks and can be confirmed by rising thyroid-stimulating hormone and falling T_4 levels six weeks after withdrawal.

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Public Health and Preventive Medicine

Vital Records as Indicators of Chronic Diseases

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One of a series of articles from western state public health departments

Vital records can be used to monitor the health of a population and to help develop an understanding of the pathogenesis of disease. In the state of Washington, vital records are used not only for legal purposes and for computing birth and death rates, but also to provide a data base for several surveillance systems. These include systems for the monitoring of birth defects and occupational mortality problems. In addition, vital records in the state of Washington have recently provided data for studies of neonatal mortality, accidents in infants, toxic shock syndrome and lung cancer in orchardists—to mention a few.

Vital records (birth, stillbirth and death certificates) routinely collected by all the states and most countries of the world are among the best data available for assessing the health status of a population. The great strength of vital registration systems is that they are complete on a population basis—that is, all deaths and most births are registered. In the United States, a licensed physician must sign the death certificate, when the death is due to natural causes. In the case of suicide, homicide or death by accidents, the coroner or medical examiner must sign the death certificate.

This registration system plus enumeration of the population during the census provides the data necessary to compute birth rate, death rate and infant perinatal and maternal mortality rates. The public health pulse of the population is taken by referring to these indexes. Most states and the federal government publish annual vital statistics reports which, over time, can point to emerging or receding health problems, and which can form a rational basis for health planning and resource utilization. In the industrialized world, mortality during infancy provides a measure of the social, economic and health status of the population. An elevated infant mortality rate readily identifies underprivileged segments of a population.

In Washington state the congenital defect information reported on birth and stillbirth records is monitored on a monthly basis by tabulating the frequency of defect by type, place of birth and month of birth.[1] This system was begun in 1968 and has been able to detect a drug-associated birth defect[2] and the sequelae of a rubella pandemic. The thalidomide disaster in Europe was producing birth defects for over a year before the drug association was recognized. This is understandable, since the defects were widely distributed in the population of births. It is hoped that surveillance of the birth registration system will shorten the time to discovery if an analogous epidemic occurs here. All birth and stillbirth records in the state pass through a data collection funnel, so if the defect is reported on the birth record and a change in frequency of defect occurs, it should be discernible.

Another use of the information routinely collected on the Washington state death record is surveillance of occupational mortality using the death record occupational statement. The death record occupational statements for all men who died in the years 1950 through 1979 and all women who died in the years 1974 through 1979 have been coded, added to the computerized death record and analyzed using a proportionate mortality ratio method.[3] This file now contains 500,000 records. Since 1980 the death record occupational statements and parental occupations on the birth record have been coded routinely.

The death record analysis has pointed to previously unrecognized occupational mortality problems that

Refer to: Beare JA, Milham S Jr: Vital records as indicators of chronic diseases (Public Health and Preventive Medicine). West J Med 1983 Aug; 139: 234-235.

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have been confirmed in follow-up studies.[4-6] The great appeal of occupational mortality studies is that occupational morbidity and mortality are theoretically preventable. The following are occupational mortality problems uncovered by this study: increased lung cancer in copper smelter workers,[4] increased pancreatic cancer and multiple myeloma in workers at a nuclear facility[5] and increased mortality due to emphysema, leukemia and lymphoma in aluminum reduction plant workers.[6]

The National Institute for Occupational Safety and Health (NIOSH) supported some of this work and is encouraging and supporting this activity in other states.

Especially important to the vital records studies is the information provided by the physicians, such as cause of death, complications of pregnancy and descriptions of congenital defects. We would therefore encourage physicians to be as specific and complete as possible in furnishing vital records information. It takes nearly as long to write "multiple congenital defects" as to list the major defects seen.

Vital records will have an increasingly important role in the future as a source of information for chronic disease studies. These studies will be only as good as the information provided on vital records by the people who fill them out.

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Articles to Read in Other Journals

Long-term Results of Prospective Randomised Study of Coronary Artery Bypass Surgery in Stable Angina Pectoris

European Coronary Surgery Study Group

Lancet

II:1173-1180, Nov 27, 1982

DISCIPLINES: Family Practice, Internal Medicine, Cardiology, Cardiac Surgery

READABILITY: Average

Results of a five-year plus follow-up of 768 men with coronary artery disease randomly assigned to receive a coronary artery bypass operation, or not, are reported by a European collaborative group. Criteria for surgical selection (such as three-vessel disease or stenosis of proximal third of the left anterior descending artery as part of two-vessel disease) or for medical regimens are evaluated.

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Traditional Chinese Medicine in China

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DR SOONG LING-LING, *Beijing*

As a fourth-year medical student, I studied traditional Chinese medicine in Beijing while rotating through several of the major teaching hospitals.

My first month was spent in a busy acupuncture clinic where a single doctor treats up to 50 patients in a morning. There are three acupuncture clinics in the Outpatient Department of Neurology at the First Affiliated Hospital of Beijing. Acupuncture needles and alcohol wipes are the only instruments used by the doctors. There is usually no diagnostic workup. With each patient the focus is on treating symptoms to restore the flow of "vital energy." For each symptom there is a formula of acupuncture points that stimulate the various "energy channels," of which western medicine has no equivalent concept.

The patients' symptoms are usually of two types: chronic pain, including low back pain and arthritic pain, and neurologic problems, such as Bell's palsy, paralysis caused by stroke, tinnitus, herpes zoster, facial tics and sciatica. Other less common symptoms include enuresis, toothache, phlebitis, insomnia, amenorrhea, anemia and constipation. Many of the patients have tried western medicine without success whereas others use combined modalities. Acupuncture is often used in combination with herbal remedies.

Treatment consists of a series of visits spaced several weeks apart. Different acupuncturists have developed their own techniques, such as the quick-poke method in which a needle varying in length from 0.5 to 10 cm is inserted and withdrawn as soon as the patient "gets the feeling." Sometimes vitamin B_{12} is injected into an acupuncture point. For those patients frightened of needles, the cup-extraction method is favored in which a burning match is thrown into a cup that is then quickly applied to the patient's skin at an acupuncture point. Treatment using heated needles, known as moxibustion, is shown in Figure 1.

Acupuncture is also widely used for anesthesia. In the Peking Women's Hospital acupuncture anesthesia has been used routinely for cesarean sections since 1970. Acupuncture anesthesia is used in 95% of all cesarean sections and in about 80% of all other gynecologic operations done in the Peking Women's Hospital. In many cases it is used in combination with a local anesthetic applied at the incision site.

For acupuncture anesthesia for cesarean sections, six acupuncture sites are used; four in the abdomen and one on each calf. These needles are connected to a small generator so that electrical stimulation is supplied during the entire operation. Usually the woman receives no sedation and is conscious throughout the operation. Though the acupuncture anesthesiologist monitors blood pressure and pulse rate, there is seldom any alteration in physiologic function during the operation.

Traditional Chinese doctors are trained in the use of herbs as well as acupuncture. A diagnosis is made on the basis of a short history and physical examination, which consists of noting the color, texture and coating of the tongue and palpating the pulse (Figure 2). The pulse, felt to represent the functioning of internal organs, is palpated with three fingers, each finger focusing on a different system. Very rarely is a stethoscope used as part of the physical examination. The herbs that are then prescribed have been determined by centuries of experience.

The herbal pharmacy in a hospital contains file-cabinet-sized drawers filled with plant, animal and insect products (Figure 3). Most pharmaceutic herbs are roots. The insides of the bamboo tree and chrysanthemum buds are used for gastric distress. A plant called borneol os (a kind of camphor) is used for herpes simplex virus infection. Cow's bezoar is used as an antipyretic. Bird excrement is used for insomnia. Some of the more exotic drugs include rhinoceros horn, hedgehog skin and chicken gizzard. A pharmacist weighs each herb according to prescription and then mixes

Refer to: Randel S, Soong L-L: Traditional Chinese medicine in China (Medicine in Perspective). West J Med 1983 Aug; 139:236-238.

Dr Randel was the first American medical student invited to do a fourth-year elective in Beijing, China. This article about her observations has been edited by Dr Soong Ling-Ling, senior professor at the Beijing Medical College.

Submitted July 26, 1982.

Reprint requests to Susan Randel, MD, Mount Zion Hospital and Medical Center, P.O. Box 7921, San Francisco, CA 94120.

them into a concoction that is brewed by the patient. Several packages are distributed—a package to be brewed and drunk each day (Figure 4).

Herbs are popular, especially among older patients, because they have few unpleasant side effects. In some cases western drugs are used in the acute stage of a disorder and then herbs are used for general strengthening of well-being. Herbs can also be prescribed concurrently with western medicines. For example, in the treatment of gastric cancer, herbs are used in conjunction with chemotherapy to potentiate the effects of the chemotherapy and to decrease side effects such as nausea.

Herbs are used with acupuncture to increase the ease of passing kidney stones. Combining these modalities acts to dissolve stones while increasing the peristalsis of the ureters. Stones as large as 8 mm in diameter (documented by pyelogram after contrast agent was given intravenously) have been passed by using this combination. Physiotherapy, acupuncture and, rarely, meperidine hydrochloride (Demerol) are used for analgesia.

Traditional Chinese physicians attend medical school and study both the basic sciences and traditional Chi-

Figure 1.—A patient being treated by means of moxibustion, a form of acupuncture in which the ends of the needles are heated.

Figure 2.—A traditional Chinese physician making a diagnosis by palpating the pulse. Pulse palpation and noting the tongue color and consistency comprise the entire physical examination.

Figure 3.—A traditional Chinese pharmacist making up a prescription of herbs.

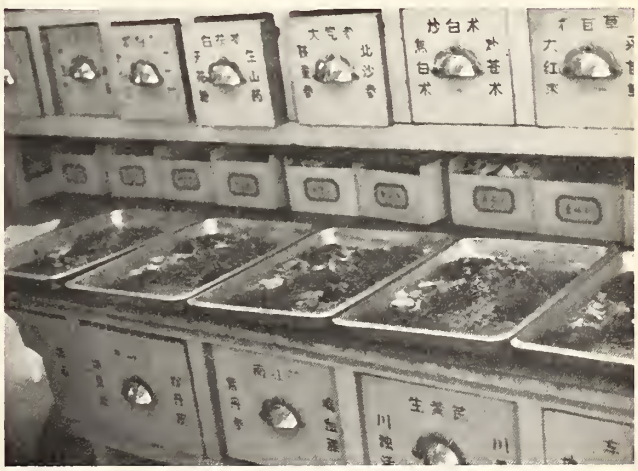

Figure 4.—Each tray in this photograph constitutes one prescription in a herbal pharmacy. Every day a pan of these herbs is brewed and the resulting tea is drunk.

nese medical theory (as well as Marxism, Leninism and English) for the first two years. The remaining three-year curriculum includes about 40% clinical western medical practice and 60% traditional Chinese medical studies. The physicians then do a three-to-four-year residency in a traditional Chinese medical department.

Figure 5.—An acupuncturist treating a patient for insomnia.

To understand traditional Chinese medicine requires setting aside one's western way of thinking about medicine. For what the Chinese call energy channel, there is no western anatomic or biologic correlate. These channels and corresponding acupuncture points have been developed through thousands of years of trial and error.

The Chinese medicine conception of functions of organs is very different from anything I learned in medical school. Though the concepts of vital energy and organ function are not modified by western thought, the Chinese are now integrating western methodology with their traditional practices. Both eastern and western medicine are used in China, either in combination or as alternative forms of therapy and diagnosis (Figures 5 and 6).

Figure 6.—A child being treated by acupuncture for enuresis.

Informed Opinion

Contingent Fees in Medical Malpractice Litigation — A Qualitative Assessment

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The medical profession has experienced high liability insurance premiums accompanied by widespread use of contingent fees in medical malpractice litigation. It is worthwhile, therefore, to assess qualitatively the merits of contingent fees, the evidence suggesting that they are associated with unjustified litigation and their implications for the medical and legal professions.

For the medical profession there have been steadily rising liability insurance premiums whose rate of increase is above that for general economic inflation.[1] Data are still being gathered on the precise impact of rising premiums on medical cost, quality and accessibility.[2,3] Nonetheless, little discussion has centered on *why* liability premium rates have risen so dramatically other than to note that claims are rising (in number and dollar amount) while insurers attempt to cover their higher risk. Meanwhile, the medical care field has adapted to the changes in professional liability through a variety of different mechanisms—paying higher premiums, practicing defensive medicine (that is, using good medical practices to reduce liability exposure), canceling insurance, self-insuring and forming cooperative insurance groups.[4,5]

Beyond the rising health cost implications of contingent fees there is an unsettling belief (among physicians) that this mechanism serves as a stimulus to promote an increased number of unjustified suits, often of nuisance value and of such a nature as to wrongfully tarnish the reputation of the defendant physicians. The objectives of this paper are to qualitatively assess the merits of contingent fees in medical malpractice litigation and to explore whether physicians are oversensitive to litigation. As the medical care field continues to address the professional liability problem, two basic health policy questions must also be addressed: What factors have supported medical malpractice litigation? What attitude should physicians adopt toward the malpractice issue?

The Concept and History of Contingent Fees

In his book *Contingent Fees for Legal Services,* published by the American Bar Association, F. B. MacKinnon defined a contingent fee as follows:

> a fee received for services performed on behalf of a client who is asserting a claim, payable to the lawyer if, and only if, some recovery is achieved through the lawyer's efforts. Its distinguishing characteristic is the negative; if no recovery is obtained for his client, the lawyer is not entitled to a fee.[6(p3)]

This legal financing method is not limited to malpractice litigation. It is widely used in American legal practice in personal injury cases of which medical malpractice is only one category.

Contingent fees typically are structured as a percentage of the final financial product of the litigation. In medical malpractice cases, this percentage has varied from 10% to 50% of the award to a plaintiff.[7] As well, they are often defined as a decreasing percentage of the recovery (for example, 40% of the first $5,000, 35% of the next $20,000 and so forth). The fee payable to an attorney is usually in addition to actual expenses incurred in managing the case. Expenses are charges billed to the plaintiff's lawyer by consultants or other lawyers, as well as out-of-pocket expenses incurred by the plaintiff's lawyer (travel expenses, for instance). Some states such as Michigan and New Jersey have established maximum contingency fee schedules allowable within the state.[7] These schedules may limit the contingent fee charged by a plaintiff's attorney, and in addition, contingent fee contracts are subject to supervision by the courts.

In contrast to contingent fees, the fee-for-service method is the conventional system of payment for legal

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services. This is similar to the fee-for-service approach used frequently in other professions, including medicine. The fee-for-service method promotes the notion that the professional "sells . . . expert advice, generally on confidential matters, where probity is essential."[8] The elements of value offered by the professional in the exchange are time, knowledge, experience and skill in utilizing those assets. The problem of quantifying these services for client pricing purposes has traditionally been solved by dividing the services into units of time or specific procedures. For example, an appendectomy by a surgeon, an office call by an internist or the preparation of a will by an attorney all illustrate the fee-for-service methodology. The majority of legal services in the United States are priced by this method, although there is widespread use of contingent fees in personal injury litigation.[9(pp193-194)]

A complete understanding of the contingent fees depends on recognizing the distinction between *champerty* and *maintenance*. Champerty is an ancient common law crime consisting of a bargain made by a person who is not a party to the suit to bear expenses of litigation in return for a share of whatever is gained in the suit. In contrast, maintenance is the officious intermeddling in a legal suit, by financially supporting the prosecution of the suit. This, too, is a common law crime. The accepted current distinction between champerty and maintenance is that maintenance refers to the financial support of a party to a lawsuit by one who has no direct interest in it, while champerty is the agreement to carry on a lawsuit in exchange for the promise of a share in the recovery. Thus, to the extent that the client's success is shared with his or her attorney there is a similarity between champerty and contingent fees.[6(pp37-38)]

The contingent fee mechanism as a system of payment for legal service is principally confined to the United States. It is illegal and unethical in the practice of law in England, France, Germany, a number of other European countries and India.[10] However, the practice is accepted in Japan, Spain and some provinces of Canada. The attitude of the American Bar Association toward it has gradually changed during the 20th century.[11] The implications of this acceptance for the medical field and individual physicians are best understood by reviewing the justification for its use.

Justification for Contingent Fee Use

Probably the most widespread and most forcefully argued justification in support of contingent fees is their social merit. They provide a mechanism for promoting the cause of justice on behalf of persons in society who could not otherwise afford legal services. It is argued that "no other system has been suggested which provides capable legal service to those unable to afford legal fees, without introducing serious risks of destroying the (legal) profession."[12] Because of the support it provides the economically indigent, the mechanism gained widespread application in the United States. It is now the major system for financing personal injury litigation. Contingent fees are also justified because of their positive motivating influence on attorneys. It may motivate attorneys to work more effectively and conscientiously on behalf of their clients by placing gross earnings at risk. The fee is dependent on the size of a client's recovery. Similar to the production worker paid on a piece rate, the greater a lawyer's output, the higher is the reward. There is a more subtle significance to this argument than mere prodding to work harder and to pursue more substantial outcomes. Unlike a factory manager who hires a piece rate worker, the legal client is not qualified to evaluate the quality of the lawyer's performance during the process of litigation. Clients inevitably develop the perception that the lawyer is performing at maximum capability because of the motivating effect of the incentive.

Contingent fees encourage skilled speculative work in many areas of legal practice that would otherwise go without attention. This has important social significance in promoting unpopular or minority causes, the resolution of which may prove to the ultimate good of society. Additionally, they can promote expeditious and cost-effective litigation. In the pursuit of a medical malpractice action using a contingent fee, every hour expended by a plaintiff's attorney represents an additional investment of resources in the case. The result may be a proportionate decrease in marginal earnings from the litigation if earnings equal a percentage of the recovery minus the time invested in the case. Therefore, it may be argued that the plaintiff's attorney will seek to bring a case to its earliest possible conclusion consistent with the client's interest. This will save judicial resources, defense efforts and the commitment of time, energy and resources by all parties involved.

Contingent fees have several other characteristics that support their use. From the perspective of a plaintiff, a suit, even one with great merit, bears risk. A contingent fee allows the plaintiff to shift some of the risk in the case to the lawyer. If the suit is unsuccessful and no recovery results, the lawyer receives no fee and the client usually incurs little expense. By contrast, the plaintiff who agrees to pay a lawyer an hourly fee suffers an even greater loss (the lawyer's fee) if the suit is unsuccessful.

Another justification for contingent fees is their enabling qualities allowing lawyers to compete as entrepreneurs in a competitive society. They do so with their assets (their skills, knowledge, wisdom, experience, time and office arrangements). They place these assets at risk with expectation of financial returns. In the case of the medical field they recognize that a medical malpractice case may have economic value. If a case has little or no economic value, a lawyer will not invest his or her assets in pursuing it. Under the right conditions (that is, a just court verdict) the outcomes are good for the lawyer, good for the client and good for society.[13]

Criticisms of Contingent Fees

Although contingent fees possess a number of redeeming values that support their use, they also have

a number of negative aspects. They introduce an element of risk into the attorney-client relationship. Under the contingent fee arrangement the attorney is involved in the case, anxiously looking toward the size of the settlement. To pursue this issue, it is necessary to examine the professional obligations of an attorney. Attorneys, like physicians, are members of a privileged, monopolistic, licensed elite. They owe a responsibility not only to themselves as entrepreneurs and to clients as consumers of legal services, but to the courts as well. There is an evident potential conflict of interest.

A review of the history of the attitudes of the legal profession towards the propriety of contingent fees and the potential conflict of interest they may stimulate, indicates that the legal profession does not totally agree about the concept. The dictates of English common law about champerty and maintenance were previously noted. There is a detectable schism in the American Bar Association's *Canons of Professional Ethics* in this regard.[9(pp394-397)] Canon ten states, "The lawyer should not purchase any interest in the subject matter of the litigation which he is conducting." Canon 12 describes a method acceptable for "fixing the amount to the fee." That method describes the usual professional fee for service based on needed time, skill, availability of lawyers, customary charges, risks and relationship to the client. Canon 13 is captioned "Contingent Fees." It reads as follows:

> A contract for a contingent fee, where sanctioned by law, should be reasonable under all the circumstances of the case, including the risks and uncertainty of the compensation, but should always be subject to the supervision of a court, as to its reasonableness.

Canon 13 was adopted by the American Bar Association in 1908 and amended to read as reported above in 1933. The concern of the organized bar is evident in the original draft of the proposed canon in 1908, which read, "contingent fees may be contracted for, but they lead to abuses and should be under the supervision of the court."[14] Finally, Canon 13 of the Boston Bar Association reflects much the same kind of reservation:

> A lawyer should not undertake the conduct of litigation on terms which make his right to reasonable compensation contingent on his success, except when the client has a meritorious cause of action but no sufficient means to employ counsel unless he prevails . . .[15(p33)]

Thus, a major argument against contingent fees is that an attorney's stake in the outcome of a case introduces an attitude toward the practice of law inconsistent with the detachment essential to the profession. It has been said that such an attitude may lead to "improper coaching of witnesses" and "groundless legal arguments designed to lead the court into error."[15(p33)] There may result an emphasis on winning that impairs the lawyer's self-restraint in negotiation and advocacy, thereby endangering the effective operation of the judicial system. This overemphasis on winning may, however, also be present with fee-for-service compensation arrangements; lawyers do not aim to lose.

Another criticism suggests that the use of contingent fees results in potential rewards of such enormous size as to encourage competitive solicitation of clients. Additionally, their use may increase the number of suits having little merit but substantial nuisance value. Ethically, of course, there are constraints on the pursuit of such cases. There is a well-defined concern in the legal system over the stirring-up of litigation. It is formally expressed in public policy and in English common law as the act of *baratry*—a crime.[16] It is interesting to note that concern about contingent fees has led to their repudiation in different legal circumstances such as divorce or payment for securing legislation or favorable administrative rulings.

There are a variety of potential divergences of interest between a plaintiff and his attorney when a contingent fee contract is used. Once the contract is drawn and the associated time and effort invested by the lawyer, the lawyer has an increasing investment in the case. Questions of who makes the decision of when to settle and for how much assume greater significance. Although the client theoretically has control over these decisions, as a practical matter the attorney usually addresses such matters—the attorney's recommendations are frequently pivotal. This is probably as it should be given the lawyer's superior knowledge of the case. With a contingent fee, however, the lawyer may become something of a managing partner. The attorney's interest in the case can impair the ability of the client to discipline or discharge the lawyer.

Moreover, contrary to the conventional wisdom, contingent fees do not assure indigents a day in court. Unless the prospects look profitable for an attorney, a client may be denied legal assistance if the contingent fee system is the only option for financing the services. The lawyer may well decline the risk of the case with low expected value, but this can be true whether or not the contingent fee approach is available. In a malpractice case or any personal injury litigation, there are two matters: liability and damages. The attorney assesses the likelihood of success on liability and the apparent damages amount, and creates an equation for deciding whether the case is worth pursuing. An attorney, if offered an hourly fee-for-service in a personal injury litigation, would have to make the same analysis in counseling the client on whether the litigation should be pursued.

If contingent fees progressively decline as a percentage of the recovery further conflict between lawyer and client is possible. Does the possible additional recovery for a client require a disproportionate amount of additional effort that is not marginally beneficial for the lawyer? Also because such a fee is payable without regard to time spent on the case by a lawyer, it may be to the lawyer's advantage (however unethical) to settle it quickly and on terms that are not in the best interests of the client. For example, if added work on the case would gross three times the cost necessary to obtain the result, the lawyer may have no financial incentive to pursue the claim further when the contingent fee is one third. In many contingent fee contracts, the fee is

graduated upward based on the stage of the proceedings at which a recovery is made (for example, 33% before trial and 40% after commencement of trial). Under these conditions, there may be a motivation to prolong the process.

Some have argued that contingent fees tend to increase clients' cost of personal injury litigation. A 1973 publication, the *Report of the Secretary's Commission on Malpractice* (Department of Health, Education, and Welfare) indicated that plaintiffs' attorneys who used contingent fees were paid at an average hourly fee of $63, while defense attorneys billing on an hourly basis were paid an average hourly fee of $50—win or lose.[17] That represents a 26% higher cost to prosecute a medical malpractice case using a contingent fee than to defend the same case using the fee-for-service method. The HEW report did not suggest that the difference was unconscionable, although the difference was labeled significant. The fee difference is rationalized as compensation for added risk (risk of loss resulting from failure to recover in a number of cases). MacKinnon noted that

> From the point of view of the individual lawyer, it appears that to earn a reasonably high income, he must not only charge a contingent fee, which takes account of the risk of no recovery at trial, but must also handle a good proportion of moderate sized claims which are settled at an early stage of the proceeding when the risk is small.[6(p182)]

MacKinnon's formula for lawyer success poses perils for clients in the following ways. First, the client will pay a higher price to compensate the attorney for risk and debt service. Second, the client's case may not be important enough to vigorously pursue because of cash flow considerations.

A noteworthy characteristic of the contingent fee system is its pervasiveness in certain categories of cases. It is common for plaintiffs' lawyers to favor this fee arrangement and, as previously noted, virtually all personal injury cases, including medical malpractice cases, are financed with it. Why do lawyers tend to favor contingent fees? One explanation is their profitability to lawyers. By contrast, where the use of contingent fees is closely supervised and regulated by courts and statutes—as is the case with worker's compensation proceedings in most states—there is sometimes a problem in finding a lawyer to represent a client.[7]

With these problems the question must be raised about alternatives to the contingent fee system. The Constitution guarantees the right of every person to a court appearance including representation by counsel in most criminal cases. A justification for use of contingent fees is the extension of that availability to cases in civil matters involving personal injury. Unfortunately, as we have seen, even this payment mechanism cannot guarantee that availability.

Alternatives to Contingent Fees

What alternatives are there to contingent fees? The real obstacle for the economically indigent is access to sufficient capital for financing a law suit. Canon 13 of the American Bar Association's Code of Ethics seems to support the conclusion that clients who can afford to obtain legal representation on a fee-for-service basis should do so.[15(p13)]

The goal of personal injury litigation as illustrated by medical malpractice suits is compensation for injuries attributable to substandard diagnosis or treatment. A frequent theory of the complaint is negligence by the health care provider. The objective of the legal action is not punishment but compensation for injury. There are parallels in other areas of personal injury in which the issue has been moved from the judicial to the administrative arena. Worker's compensation in many states is an example of this transition. The objective of worker's compensation is to build into the employer-employee relationship a means of compensation for work-related injury on a no-fault basis. In effect, worker's compensation builds the cost of work-related injury into the price of producing the good or service. It defines a procedure for evaluation of the degree of injury. It defines a process by which the claim can then be settled without resort to the judicial adversary process. Fault is not a primary issue. The injured party is assured that the case can be adequately pursued regardless of financial status. All parties have access to the judicial process if dissatisfied with administrative results.

Medical adversity insurance is a form of no-fault insurance which has been proposed to protect all health care consumers against the unfortunate events that can occur in any medical encounter.[18] It is proposed as a low-cost form of insurance that would indemnify a health care consumer against the cost of injury arising out of the medical diagnostic and therapeutic process. If fully implemented, it would obviate contingent fees in medical malpractice litigation because the injured patient would have no immediate need for legal assistance. Any claim would be processed as an insurance claim. From the standpoint of an injured person, the problem is simpler because only injury or harm need be shown. Negligence on the part of the health care provider is not a requirement for compensation. The objective of compensation for the injured would be served by this system. There are, however, problems with medical adversity insurance. Not all adverse events are covered so there could be many situations in which traditional liability cases would be brought. Also there are very serious difficulties in determining whether the harm suffered is a result of the case or is a continuation of the disease process or injury that brought about the need for medical care in the first place. These issues are fertile grounds for litigation.

Another alternative to contingent fee arrangements in the United States has been considered by the Royal Commission on Legal Service in Great Britain. An objective of the Commission is to eliminate financial barriers to the pursuit of a suit for personal injury. The Commission proposed the establishment of a "contingent legal aid fund."[16] It would be designed specifically

to do away with the deficiencies of the American system of contingent fees. As an agency, it would be interposed between the client and the lawyer, leaving the former free to exercise independent judgment. Once a claim had been entered, it would be submitted to a committee of lawyers charged with determining whether grounds exist for the case. The plaintiff would then be free to select a lawyer. The contingent legal aid fund would then pay the plaintiff's lawyer on a fee-for-service basis regardless of the outcome. Upon success, the plaintiff would be required to pay over to the fund the predetermined contingent fee. It has been estimated that the contingent legal aid fund would initially require government capitalization, but that it would be self-sustaining within five years. The principal merit credited to this proposal is elimination of the cost barrier to the plaintiff, while remaining free of the champertous-like relationship that may result from the contingent fee contract between lawyer and client.

Implications for Physician Attitudes

Physicians may be overly sensitive to the impact of malpractice litigation. As a group, they would probably admit that contingent fees help clients pursue a claim with minimal financial risk to the clients. Physicians who are aware of the mechanics of this fee mechanism would also admit that it permits indigent persons a better access to legal services. In reality because malpractice claims have high potential for producing income, "legal aid" programs must typically refer these cases to the private bar. Today many of the publicly supported legal assistance programs are on precarious financial ground and may not be able to afford the luxury of passing up the kinds of fee generating cases they have traditionally. However, it is clear that contingent fees have had the effect of making legal services more generally available by (1) freeing "legal aid" resources from malpractice cases so that they can be directed toward non-fee generating cases and (2) making the fee generating malpractice cases of clients otherwise unable to afford legal services attractive to members of the private bar. Thus it is clear that the existence of contingent fees results in more litigation than would occur under an exclusively fee-for-service system. Physicians are, understandably, not pleased.

Physicians should also recognize that the contingent fee system is a practical approach to financing legal services for many who are injured. Nonetheless, there are important defects in the system that raise serious questions about its continuous use in financing medical malpractice litigation. However, simply eliminating it is not the answer. The economically indigent must have access to the courts. Although not assuring such access, it does provide an avenue, but other avenues need to be explored. For example, efforts might profitably center on altering contingent fee arrangements to minimize nuisance suits, or on creating new forms of arbitration outside the courts.

The preceding discussion identifies two problems. First, the contingent fees that are so widely used in American personal injury litigation possess a number of limitations that can result in legal abuse. Second, the present judicial system fails to provide all persons access to court. While not all personal injury plaintiffs are poor, the legal profession has promoted a system in which many are represented on a contingent fee basis. Physicians are encouraged to understand the factors that led to this state of affairs, and with that understanding avoid developing an unhealthy paranoia that the legal system has conspired against them.

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Medical Schools of the West

Stanford University School of Medicine

SHIRLEY KRAUS, *Stanford, California*

Stanford University's School of Medicine is a pioneering institution. Not only is it the oldest medical school in the West, but its faculty members continually break new ground in the medical field. Stanford has led the way in providing a medical education that traditionally and consistently has been excellent. The tradition has been challenged throughout the years by changes in society and in the medical profession itself, as well as by the school's geographic location, physical facilities, administrative policies, curriculum and, of course, faculty and students. Like all medical schools today, Stanford faces new challenges brought about by pressures on society. Some of the issues include the increasing scarcity of funds available to support schools and students, state and federal legislation affecting the medical field and the national trend towards revising the entire health care system. But Stanford rises to the challenge. It continues to live up to its reputation as one of the nation's finest medical schools—growing with the profession and combining to the utmost the academic, research, clinical and administrative expertise of its faculty. Students coming to Stanford have the opportunity to obtain their medical education in a sophisticated environment and among faculty who are constantly contributing to the progress of medicine.

The medical school each year accepts 86 students from nearly 6,000 applicants. Dedicated to providing equal opportunity for medical education, the school leads the West in this regard: each class consistently has the highest percentage of minority and disadvantaged students.[1] This enables the school, the profession and ultimately society to benefit from a diversity of backgrounds and ideas.

Stanford was the first to introduce the philosophy that medical school is a graduate program in which students are responsible for acquiring an identifiable body of knowledge, in addition to having maximum opportunities for independent study and research, modified in accordance with their career objectives.[2] Students are faced with a curriculum intended to provide a balance of "essential" courses—those constituting a core of knowledge—and various elective courses, but with enough flexibility that they are able to tailor their educational program to meet their individual circumstances. The curriculum is monitored by the office of the associate dean for education, newly created in response to the changing needs of students. To graduate, students must be enrolled for a minimum of four years and must pass two-part examinations given by the National Board of Medical Examiners.

Students are given the financial assistance they need, thanks to the generosity of the numerous private donors, including the Stanford Medical Alumni Association. They have the opportunity to enroll in special programs as well, such as the Alumni Association's Medical Scholars Program, or the Medical Science Training Program. Stanford is one of the few schools that to date have not allocated general funds—which in 1980-1981 amounted to almost $76 million including research funding—for financial assistance.

The school encourages students to find meaningful jobs in conjunction with their course work—a unique aspect pioneered by Stanford. Not only does this help students financially, but their schooling is enriched through experience in research, teaching and patient care.

Faculty members, most of whom are involved in sponsored research, provide students much of the work experience. The relationship is mutually beneficial; faculty use the students' help—as laboratory assistants, for example—while students have the opportunity to work with world-renowned physicians. The educational programs' success can be seen by the fact that more than 75% of the graduates consistently get their first or second choice of house-staff positions.

Stanford has two Nobel laureates on its faculty. Arthur Kornberg received the Nobel prize in 1959 for his work in synthesizing DNA in a test tube. In 1980 Paul Berg was awarded the Nobel prize for his work on nucleic acids with particular reference to re-

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combinant DNA. Joshua Lederberg, now president of Rockefeller University, received the Nobel prize in 1958 for work done at Stanford.

Many of the 562 faculty members have brought eminence to the school through their investigative programs in areas including genetics, anesthesiology, pharmacology of anesthetics, clinical pharmacology, immunology, oncology, the neurosciences, structural biology, radiobiology, nuclear medicine, cardiology, gynecology and obstetrics, surgery and psychiatry. Faculty members have shown an exceptional ability to combine academic research with clinical skill and empathy, allowing them to make great strides in finding new treatments—and sometimes cures—for many fatal diseases.

For example, Henry S. Kaplan, MD, and Saul A. Rosenberg, MD, recently completed 20 years of research in the treatment of Hodgkin's disease. In all, 90% of their patients have survived for at least five years following treatment. Stanford has also led the field in the treatment of patients with other lymphomas. The management of high-risk pregnancies and infants is one of the obstetrics and gynecology department's main focuses. Under the direction of Philip Sunshine, MD, the pediatrics department has one of the most advanced intensive care nurseries in the country, in which 98% of premature infants survive. The department leads in the treatment of blood disorders in infants as well. Stanley Cohen, MD, in the genetics department, pioneered the development of the molecular cloning technique that has made advances in genetic engineering practical. Ronald Levy, MD, leads in research with monoclonal antibodies. Stanford also leads in interferon research, and the cardiovascular surgery department, led by Norman E. Shumway, MD, has one of the most successful heart and the only heart-lung transplant programs in the world. Since Shumway started the program in 1968, more than 270 patients have undergone heart transplants. About 50% should live about five years or more—many returning to active, productive lives—compared with virtual certainty of death within a year without the operation. At Stanford 14 heart-lung transplants have been done as well.

Besides their involvement in the medical school, students, residents and postdoctoral fellows are able to study in the other two components of the Stanford University Medical Center: the Stanford University Hospital (Figure 1) and the Stanford University Clinics. The medical center, headed by Lawrence G. Crowley, MD, Vice President for Medical Affairs, is the umbrella corporation for the separate components. The school is run by Dean Dominick P. Purpura, MD, and the hospital is run by Director Sheldon S. King. Clinic policies are determined by the Faculty Practice Plan Committee, and carried out by the clinics' director, Donald Tower.

More than 80 clinics serve as "doctors' offices" for the faculty members through the Faculty Practice Program. Independently run since January 1982, the clinics give faculty members the chance to keep up their clinical skills, while satisfying the needs of the community. The outpatient clinics offer a variety of high-quality medical services. In fiscal year 1980-1981, more than 134,000 patients visited the clinics. The revenue, which in that year was more than $34 million, is the source for faculty salaries and general operating costs of the school.

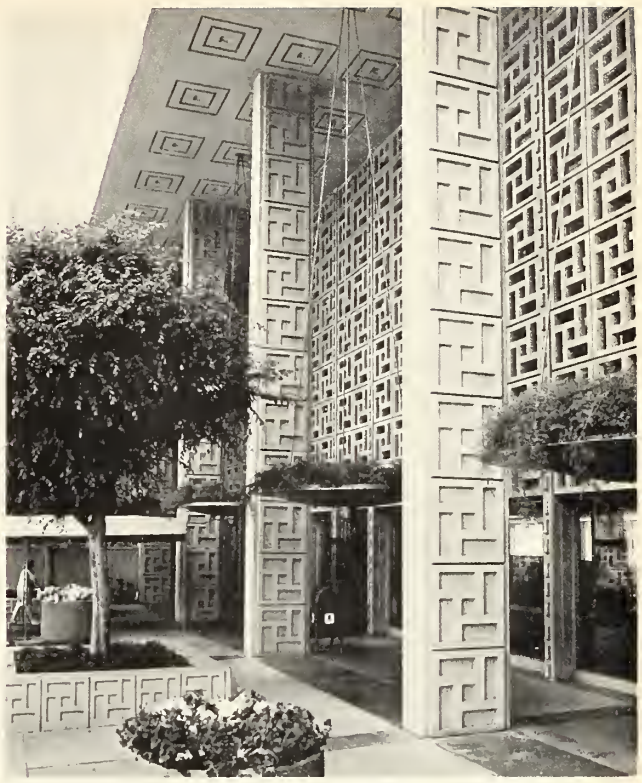

Figure 1.—The front of the Stanford University Hospital, Palo Alto, California.

Stanford University Hospital is owned by Stanford University and operates as a separate corporation without tax support or subsidy from the university. It provides high-quality patient care for the Palo Alto (California) community and surrounding areas and, in some specialties, for patients from all over the world. It is staffed by faculty and community physicians, as well as 415 house staff and more than 1,300 registered nurses. With 663 licensed beds in 1980-1981, the total patient census was more than 24,500, with almost 182,500 days of care. The average patient stay was 7.4 days. The emergency department is also active, with more than 26,500 visits during the same year. The total revenue for the year was about $129 million.

The medical school also has several affiliated teaching hospitals, including Children's Hospital at Stanford, with 60 beds for infants, children and adolescents; the Santa Clara Valley Medical Center, with 641 beds and more than 120,000 outpatient visits; the Palo Alto Veterans Administration Medical Center, with 1,437 beds, and Kaiser Permanente Hospital in Santa Clara, California.

Almost 1,400 physicians at the various hospitals volunteer to teach medical students, thus expanding

even further the students' opportunity to benefit from clinical physicians' guidance and expertise.

Historical Highlights

The medical school started as the Medical Department of the University of the Pacific, chartered in 1858 as the Far West's first medical school.[3] Dr Elias Samuel Cooper began teaching in the top story of his offices near Mission and Third Streets in San Francisco. By 1864, there had been 29 students graduated and another 22 were enrolled. In 1882 the faculty members of what had since become the Medical College of the Pacific formed yet another institution—Cooper Medical College, which, along with its hospital, was built with funds from Dr Levi Cooper Lane on Clay and Webster Streets in San Francisco. In 1908 the Stanford University Board of Trustees adopted Cooper Medical College as Stanford's School of Medicine and it became part of Stanford University.

For the first 50 years, the faculty conducted preclinical instruction at the Stanford campus in Palo Alto, sending students to San Francisco for their clinical instruction. The school pioneered many policies considered innovative. One such was a decrease in required course work, allowing 100 hours for electives during students' first four years.

In spite of the turmoil caused by World War I and the Depression, the medical school grew to include 15 interns and 21 residents by 1931. Tuition was $115 each quarter. By 1933, the student body increased to 60, and the school operated smoothly until World War II. Like all medical schools, Stanford went on a continuous teaching program known as the nine-nine-nine plan. About a third of the faculty of nearly 60 served in the military. Immediately after the war, the house staff grew to 17 interns, 49 residents and 38 fellows.

Since its establishment, those associated with the medical school had continually discussed uniting the preclinical and clinical teaching programs. But a controversy existed about whether to locate in San Francisco or Stanford. Finally, in 1953 the Stanford Board of Trustees announced its intent to establish the medical school on the university campus, causing great dissent among the ranks.

During the next four years, the board of trustees took all the necessary steps to bring the school together. The university and the city of Palo Alto agreed to construct and jointly own and operate the Palo Alto-Stanford Hospital, to be run by a committee made up equally of Palo Alto and university representatives. The board also agreed with the Veterans Administration to build extensive hospital facilities for use in Stanford research and teaching, on land purchased from Stanford. By September 1956, ground had been broken for the Stanford University Medical School campus. That year tuition increased to $355 each quarter. In 1959 the school moved from Clay and Webster Streets in San Francisco to the Stanford campus. Said former Dean Loren "Yank" Chandler, MD, "The old school as it has been known, will close this summer. A new school, new in location, philosophy, objectives, curricula and with many new faces on the faculty, will be born in September 1959 on the Stanford campus. The King is dead. Long live the King!"

The move to Stanford marked the beginning of a constant state of transition and improvement for the medical school. The original facility consisted of seven buildings under one roof designed by architect Edward

Figure 2.—View of Sherman Fairchild Building, which is part of the medical school, taken from Alumni Green.

Figure 3.—Students studying beside the Boswell Building near the Stanford University School of Medicine. The bench and marble plaque were installed by former students.

Durell Stone. Since then, the school has grown to include a Clinical Sciences Research Building and the Sherman Fairchild Building (Figure 2), which houses laboratories, an auditorium with a capacity of 400 and the departments of structural biology, neurobiology and medical microbiology.

By 1969 the faculty numbered almost 300 and had long since changed from a "geographic" to a "true" full-time basis. The number of voluntary clinical faculty reached about 800 and the house staff about 260.

Over the years students found a number of changes in the educational program. With the move to the Stanford campus, the medical school pioneered a new curriculum known as the Stanford Plan—the most striking feature of which was that it was a five-year program, with increased portions of free time as well as built-in elective time to complement the core material. About ten years later, the curriculum was once again restructured to resemble more closely what is available today.

The dramatic growth of the medical school made it apparent that the hospital organization, as originally established in the 1950s, had numerous inadequacies. One administration simply could not serve two owners. The attempt to do so continually caused operational and planning difficulties. Thus, studies were begun to determine how to establish a *university* hospital. Negotiations between the city and the university began in 1968. The city agreed to sell all of its hospital facilities to the university. In turn, the university agreed to provide appropriate patient care facilities for the community and surrounding areas and to provide access, with a unified medical staff, to community physicians.

In July 1968, the Stanford University Hospital became an entity, and the board of trustees of the university designated the entire center—including the school and hospital—which until 1982 incorporated the clinics —as the Stanford University Medical Center.

Looking Ahead

The medical school continues to pioneer in new directions in response to a constantly changing profession and its role in society. In the planning stages is a Center for Molecular and Genetic Medicine, which will draw upon the fields of molecular biology, genetics and the impact of the developments in these areas on the clinical problems of medicine, neurology, psychiatry and pediatrics. The medical center is providing adequate facilities for growth. For example, a cardiovascular research center is under construction to accommodate the success and expansion of programs.

Biotechnology—and the probability of relationships between medicine and industry—marks the beginning of yet another era, despite many concerns and potential conflicts of interest that must be solved. Stanford has introduced efforts to investigate and find solutions to any problems in order to promote these new areas.

Continued growth, program development and expanded research are of primary importance. Faculty members have been, and continue to be, competitive in attracting funding for research. In 1980-1981, for example, the medical school faculty received 375 awards, for a total of more than $53 million for research.

The hospital is undergoing major physical changes, as well. A $123.9-million hospital modernization program is under way, renovating and adding to the medical center. The cost is proof of Stanford's commitment to providing physicians the opportunity to practice, and students to learn, in a modern environment. Finally, Stanford will have a real "teaching" hospital, a facility designed specifically to meet the needs necessary for combining community and tertiary care with the educational needs of a teaching institution.

Whether in the area of curriculum, physical facilities or any component of the medical center, Stanford has always been innovative, keeping in mind its reputation for excellence. Maintaining the quality of the medical school has always been, and continues to be, a challenge to a dynamic, dedicated and farsighted faculty. The greatest portion of this challenge, perhaps, is presented by the students (Figure 3). To guide and inspire students to be able to succeed in making their own contributions to the medical field may be the ultimate goal. The medical school faculty has so far successfully achieved this goal and is confident it will continue to do so.

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The Changing Face of Medicine

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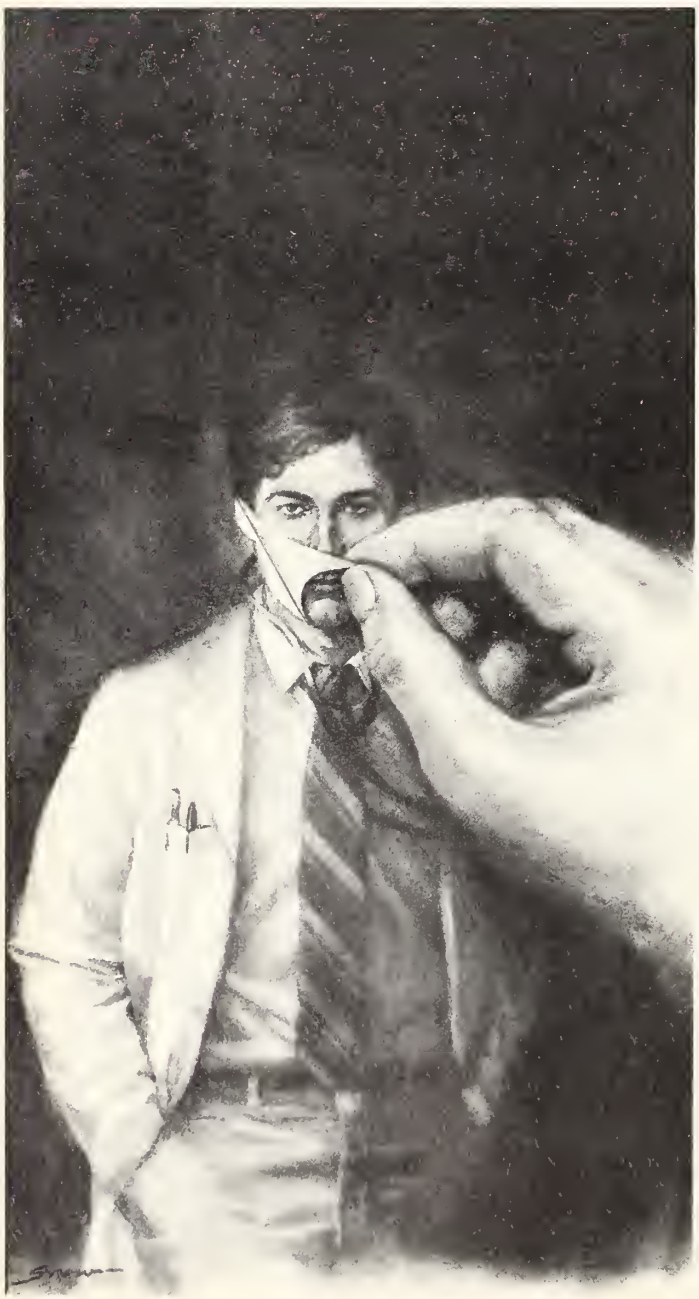

WEDNESDAY — SEPTEMBER 14

House of Delegates meetings & dinner

THURSDAY — SEPTEMBER 15

Opening Session

David N. Sundwall, M.D., Staff Assistant for Labor and Human Resources Committee
U.S. Senate, "Government & Medicine"

Richard J. Frey, M.D., Leader in competitive aspects of medicine — Preferred Provider Organizations
"Competition in Medicine"

Larry Lewin, noted health planner and author of Lewin Report
"Changing Relationship of Physicians & Hospitals"

Jack N. Behrman, Ph.D., Luther Hodges Distinguished Professor of Business Ethics
"Ethics of Rationing Health Care in 1980"

Activities

Golf tournament — sponsored by Smith Management Corp.
Tennis Tournament
Presidents' Reception & Dinner

FRIDAY — SEPTEMBER 16

University of Utah School of Medicine
"The Effect of the Revolution in Biomedical Sciences on Medical Practice"

Morning Session

G. Richard Lee, M.D., Dean of University of Utah School of Medicine
Introduction: "Medical Training — a Look to the Future"
Mark H. Skolnick, Ph.D. — "Cancer Genetics in Utah"
Mark Leppert, Ph.D. — "Molecular Genetics in the Human"
Ellie Ehrenfeld, M.D. — Genetic Engineering
"Future of Virus Vaccines"
David G. Bragg, M.D. — "New Advances in Medical Imaging"
Meet the Professor — Round Table Discussion

Afternoon Session

William Odell, M.D. — "Ectopic Hormone Production"
Richard Baringer, M.D. — "Herpes Simplex Virus and the Nervous System"
Zell McGee, M.D. — "The Gonococcus: A Model for Prevention of Infections at Mucosal Surfaces"
William R. Keye, Jr., M.D. — "In Vitro Fertilization"
Meet the Professor — Round Table Discussion

Concurrent Friday Program

Utah Ophthalmological Society
Morning and Afternoon Sessions

G. Richard — "Uveitis"
O'Conner, M.D.
David L. Fisher, M.D.

Utah Obstetrical and Gynecological Society

Morning Session

John J. Sciarra, M.D. — Guest Speaker

A. Marsh Poulson, M.D. — "In Vitro Fertilization: Clinical Aspects"
William R. Keye, Jr., M.D. — "Gynecologic Laser Surgery"
Julian DeLia, M.D. — "Low Dose Oral Contraceptives"

Luncheon
6th Annual Skaggs-Alpha Beta Luncheon — Governor Scott M. Matheson

Evening
USMA BBQ with families

SATURDAY — SEPTEMBER 17

Opening Remarks
W. Knox Fitzpatrick, M.D.
UMIA Medical Director

John H. Snow Memorial Lecture
David S. Rubsamen, M.D., L.L.B.
A consultant on medical aspects of litigation
Holds degrees from Stanford University in medicine and law. Editor of "Professional Liability Newsletter"

Panel Discussion
"What Are We Doing Wrong?"
Panel Members:
David S. Rubsamen, M.D., L.L.B.
Elliott J. Williams, J.D.
W. Knox Fitzpatrick, M.D.
Merrell A. Godfrey, M.D.

Concurrent Sessions
Problems with childbirth
Problems with surgical practice
Problems with non-surgical practice

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History of Medicine

Neurologic Aspects of Human Anomalies

CDR PAUL D. MORTE, MC, USN, *Portsmouth, Virginia*

The history of medicine is replete with unique or unusual patients who, although the subjects of cruel quirks of nature, contributed greatly to the knowledge of disease. Most students of neurology are familiar with Dr Harlow's famous patient, Phineas P. Gage, who was changed from a temperate, industrious foreman to a sociopathic vagabond after an explosion sent a 3½ foot iron tamping rod through his left frontal lobe.[1] Harlow reported that after 12 years of capricious behavior and unstable employment, including a brief stint on exhibit with his "iron" at Barnum's American Museum, Gage died in status epilepticus.[2,3] The Gage case illustrated that although profound frontal lobe trauma might spare the intellect and motor system, personality would be affected. Many of the human oddities, or "prodigies" as they now prefer to be called, were required to earn their living by exhibiting themselves in sideshows. Harvey Cushing was fascinated by circus sideshows, especially the giants, midgets and fat ladies. He befriended these "prodigies," keeping in touch with them over the years, and utilized the midgets to test the effect of growth hormone.[4]

Some of the more famous human curiosities include Charlie Byrne (the Irish Giant), Charles Stratton (Tom Thumb), Isaac Sprague (the Skeleton Man), James Morris (the Elastic Skin Man), Eng and Chang Bunker (the Siamese Twins) and John Merrick (the Elephant Man). An examination of their histories provides some interesting facts about the neurologic aspects of their disorders, as well as adding color to medical history because they crossed paths with some of the greats of medicine. But, more important, many of their stories are inspiring and present a lesson in human courage and dignity in the face of overwhelming odds.

One of the most interesting of the human curiosities was Charlie Byrne of Ireland, born 1761. In 1782, after serving as a porter to George III at St James's Palace in London (giants and midgets were collected by royalty), he placed himself on exhibit as the tallest man in the world, claiming his height was 8 ft 4 in.[5] He came to the attention of John Hunter, the most gifted surgeon of 18th century England, who had a passionate curiosity about experimental science. Hunter conducted numerous experiments, including inoculating himself with pus obtained from a patient with gonorrhea so that he could observe first hand the progression of the disease.[6] He wished to add the Irish Giant to his personal museum which was to number more than 13,000 specimens. Byrne was so terrified that his body might be boiled down in the surgeon's kettle, however, that on his deathbed at the age of 22 he got a fisherman to agree to bury his body in the Irish Sea. (Death was attributed to alcoholism, although it probably was more directly related to acromegaly.) Hunter managed to acquire the body through a £500 bribe to the undertaker and the giant became the centerpiece of the Hunterian Museum. More than a century later, Harvey Cushing, fascinated by the pituitary, persuaded the curator of the Hunterian Museum to remove the Irish Giant's calvarium. As expected, the sella turcica was notably enlarged, and there was evidence of significant extrasellar extension.[4] Presumably, Byrne had a chromophobic or acidophilic adenoma of the pituitary. His 92¾-inch (7-ft 9-in) skeleton[7] (giants exaggerated their heights), as well as the kettle in which it was boiled, can still be seen at the Royal College of Surgeons in London (Figure 1).

Pituitary hypofunction is the cause of approximately 10% of the cases of dwarfism.[8] (Actually these persons are considered by laymen to be "midgets" rather than dwarfs since their body proportions are normal.) Such hypofunction may occasionally be associated with a craniopharyngioma or suprasellar cyst but more often reflects idiopathic multiple pituitary hormone deficiencies or isolated growth hormone deficiency. The latter may occur sporadically but usually is familial and transmitted as an autosomal recessive disorder. Charles Sherwood Stratton, the diminutive General Tom Thumb and the most famous dwarf in history, is probably an example of idiopathic pituitary hypofunction. He was discovered at age 5 by P. T. Barnum in 1842 at which time his height was 2 ft

Refer to: Morte PD: Neurologic aspects of human anomalies (History of Medicine). West J Med 1983 Aug; 139:250-256..

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1 in and weight was 16 lb.[9] Thumb became a tremendous success, appearing before the royalty of Europe including Queen Victoria at Buckingham Palace, as well as President Polk at the White House. He earned millions, allowing him to indulge in his passion of thoroughbred horse racing and yachting. The wooing of his future midget-wife Lavinia, which resulted in fisticuffs with his equally diminutive rival, Commodore Nutt, was well publicized. Following their spectacular wedding at Grace Church, New York, which was attended by several thousand guests, the Thumbs were given a reception at the White House by President Lincoln.

As might be expected in pituitary dwarfism where the epiphyses of long bones remain open, Thumb continued to grow slowly far beyond the usual age of puberty, ultimately reaching a height of 3 ft 4 in. Also he had the typical puffy appearance of the skin with truncal obesity (eventually weighing a portly 70 lb) associated with hypopituitarism and probably reflecting a concomitant hypothyroidism. Although he and Lavinia failed to produce offspring (despite a hoax perpetrated by Barnum),[5] pictures of him before his death at age 45 showing a beard and mature male pattern of scalp hair indicate that he had attained some sexual development (Figure 2).

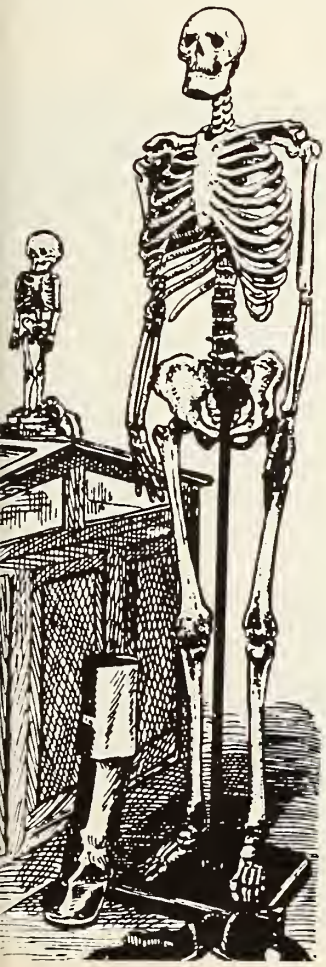

Figure 1.—Skeleton of the Irish Giant mounted alongside the skeleton of Caroline Crachami, the Sicilian Dwarf (19-in tall). (Taken from *Anomalies and Curiosities of Medicine* by George M. Gould, MD, and Walter L. Pyle, MD.[5] Copyright by W.B. Saunders and by The Julian Press, Inc. Used by permission of Crown Publishers, Inc.)

Certainly the bravest dwarf in history was Geoffrey Hudson who was presented in a pie to Henrietta Maria, Charles I's wife, in 1627 when he was 8 years old and about 1 ft tall.[5,0] His appearance in the painting by Van Dyke "Queen Henrietta Maria and Her Dwarf Geoffrey Hudson" (1635) suggests that he was a pituitary dwarf and strikingly handsome, lending credence to his boast of being able "to make married men cuckolds without making them jealous" (Figure 3). He served as a courier to the Stuarts and killed in a duel a gentleman named Crofts who had the misfortune to ridicule the dwarf's bravado. At age 30 Hudson was only 18 in tall but afterwards his height rapidly increased, ultimately to 45 in. He attributed this growth spurt to the indignities that he experienced while being held captive for ransom by Barbary Coast pirates. In actuality pituitary dwarfs often follow this postmaturity growth pattern. He died at the age of 63 after being imprisoned for taking part in a "papist plot."

Tom Thumb, Lavinia, Commodore Nutt and Geoffrey Hudson were all probably victims of pituitary dwarfism. On the other hand, the most common cause of disproportionate dwarfism is achondroplasia.[11] This is an autosomal dominant disorder (often sporadic) of endochondral bone formation resulting in skeletal deformities and neurologic abnormalities.[12] Because the base of the skull is the only portion preformed in cartilage, its growth is arrested whereas there is over-

Figure 2.—General Tom Thumb and Lavinia Warren. (Courtesy of Circus World Museum, Baraboo, Wisconsin.)

growth of the calvarium resulting in brachycephaly. In addition to macrocephaly, which is usually accompanied by mild ventricular dilatation without clinical evidence of increased intracranial pressure, there is occasionally significant hydrocephalus probably resulting from cerebrospinal fluid obstruction at the foramen magnum level. Vertebral abnormalities include exaggeration of the lumbar lordosis, unstable and recessed vertebral bodies and a stenotic spinal canal especially in the lumbar region. As a result, it is reported that in 40% of adult achondroplastic dwarfs dysfunction of the cauda equina develops.[11]

The muscular dystrophies have also produced human curiosities. Skeleton man Isaac Sprague, "The Original Thin Man," related that he was well until age 12 when he began to lose weight rapidly despite an excellent food intake. He exhibited himself at P. T. Barnum's New American Museum, New York City, in 1868 and was examined that year at the Boston Zoological Institute by Oliver Wendell Holmes.[9] Holmes is so well known for his literary works, such as *The Autocrat of the Breakfast Table,* that many do not realize that he was a prominent physician whose essay "On the Contagiousness of Puerperal Fever" (appearing five years before Semmelweis' work) is a medical classic.[13] Dr Holmes diagnosed Sprague to be suffering from "excessive progressive muscular atrophy." Actually Sprague, 5 ft 4 in tall and weighing only 52 lbs at age 48, was probably a victim of the autosomal recessive limb-girdle form of muscular dystrophy. The autosomal dominant facioscapulohumeral form is a less likely diagnosis because there was no family history and no facial involvement.

Other "skeleton men" may have suffered from infarction, tumor, trauma or infection of the adenohypophysis resulting in pituitary cachexia (Simmond's disease), anterior hypothalamic gliomas producing emaciation despite a ravenous appetite or motor neuron disease. Progeria, the Hutchinson-Gilford syndrome of premature senility, arteriosclerosis, dwarfism and wizened appearance,[14] may be another cause of this curious phenomenon. Cerebrovascular infarctions and angina may occur in the first decade, and the average age of death is 16 years as a result of coronary artery occlusion. A likely example was the little Welshman Hopkin Hopkins, exhibited in London as a natural curiosity in the 1750s. He died at the age of 17 "of mere old age and gradual decay" and never weighed more than 17 lb.[5]

Other historical living "skeletons" of uncertain pathogenesis included Claude Seurat, whose cardiac contractions were plainly visible because the distance from his sternum to his vertebral body was less than 3 in.[5] Exhibited in England in 1825, Seurat's daily food intake of a mere penny roll and a small quantity of wine stands in contrast to the excellent appetite of men like Sprague and James W. Coffey. The latter was known as the "Skeleton Dude" because of his outlandish costumes and weight of 70 lb (Figure 4 and 5).[9]

At the opposite end of this spectrum of deformity are the circus strong men, some of whom suffer from a

Figure 3.—*Queen Henrietta Maria and Her Dwarf Geoffrey Hudson* by Van Dyke (1635). (Courtesy of National Gallery of Art, Washington, DC; Samuel H. Kress Collection.)

Figure 4.—J. W. Coffey, Living Skeleton. (Courtesy of Hertzberg Circus Collection, San Antonio Public Library, San Antonio, Texas.)

Figure 5.—J. W. Coffey, Living Skeleton. (Taken from *Anomalies and Curiosities of Medicine* by George M. Gould, MD, and Walter L. Pyle, MD.[6] Copyright by W.B. Saunders and by The Julian Press, Inc. Used by permission of Crown Publishers, Inc.)

disorder classified with the muscular dystrophies, namely the autosomal recessive form of myotonia congenita (Thomsen's disease).[15] This relatively benign condition is characterized by tonic painless spasms of voluntary muscle and hypertrophy that can reach Herculean proportions. Unfortunately, strength is not proportional to muscle bulk, perhaps as a result of the associated mild distal weakness and the difficulty in relaxing antagonists.

Other favorites of circuses are "elastic skin men," otherwise known as "India rubber men" (Figure 6). James Morris was one example. A barber before he began earning $150 per week with the Barnum and Bailey Circus in the 1880s, he was able to pull the skin of his chest to the top of his head as a result of its hyperelasticity.[9] Of the heritable connective tissue disorders, this autosomal dominant Ehlers-Danlos syndrome is the oldest reported, being first described in 1682.[16] Clinical manifestations besides hyperelasticity include skin and blood vessel fragility in which slight injury may produce gaping wounds, hemorrhagic tendencies and easy bruisability, hyperextensible joints conducive to feats of contortionists as well as to habitual dislocations and dissecting aneurysm of the aorta. In addition, weakness of the media of intracranial arteries leads to aneurysms in the subarachnoid space.

No human oddity attracted more attention from the medical profession than the Siamese Twins, Eng and Chang Bunker. Upon arrival from Thailand in 1829, they were examined by John Collins Warren, professor of surgery at Harvard Medical School, later credited with being the first physician to use ether in a surgical procedure.[17] He advised against surgical separation because the interconnecting ligament, 4 in long and 8 in around, might contain a common peritoneal cavity. Evidence to suggest this was the observation that coughing or the Valsalva maneuver caused protrusion of abdominal viscera into the ligament. Warren noted that Chang was more dominant and irritable in temperament, whereas Eng was passive and mild mannered. Chang, who stood to the left and with his arm over Eng, had severe scoliosis (Figure 7).

After exhibiting themselves for a decade in Europe and the United States, the twins settled in Mount Aire, North Carolina, becoming prosperous, slave-owning farmers and scandalizing the community by marrying a local clergyman's two daughters. This harmonious union produced a total of 21 offspring—11 presumably by Eng and 10 presumably by Chang. Each family had its own house at which the twins spent alternating three-day periods. Mark Twain, a contemporary known for his interest in the bizarre, satirized the Siamese Twins,[18] writing that "During the war they were strong partisans, and both fought gallantly all through the great struggle—Eng on the Union side and Chang on the Confederate. They took each other prisoners at Seven Oaks. . . ." Concerning the courting of the clergyman's daughters, Twain wrote,

> Both fell in love with the same girl. Each tried to steal clandestine interviews with her, but at the critical moment, the other would always turn up. By and by, Eng saw, with distraction, that Chang had won the girl's affection; and, from that day forth, he had to bear with the agony of being witness to all their dainty billing and cooing.

As the twins aged, they became apprehensive of the fact that at the death of one, the other would be attached to a cadaver. This led to further consultations with leading medical authorities including Sir James Young Simpson, professor of medicine at Edinburgh, who introduced the use of chloroform in obstetrics; Rudolf Virchow, founder of cellular pathology, and Sir William Ferguson[19] of the Royal College of Surgeons. However, medical opinion remained unanimously against surgical separation as long as both were alive. A few years later, at the age of 59, while playing chess, Chang had a stroke resulting in a right hemiparesis. An interesting walking prosthesis was devised by their attending physician consisting of a crutch placed under Chang's paretic right arm and a leather strap that sup-

Figure 6.—Elastic Skin Man. (Courtesy of Circus World Museum, Baraboo, Wisconsin.)

Figure 7.—The Siamese Twins, Eng and Chang, with wives and two of their 21 offspring. (Courtesy of Circus World Museum, Baraboo, Wisconsin.)

ported his right foot and was carried by his brother. Three years later, Chang died during sleep and Eng awoke to discover that he was now attached to a cadaver. He immediately began to complain of severe cramping pain in all extremities and became diaphoretic and dyspneic. Within two hours he also died.

The family agreed to a limited postmortem examination, which was done by William H. Pancoast, professor of surgical anatomy at Jefferson Medical College in Philadelphia.[20] It was found that the twins had joined livers, thus confirming that any attempt to separate them during life would have been fatal. Although examination of the brains was forbidden by the family, it was postulated that Chang's cause of death was an intracerebral hemorrhage, and that Eng probably died from syncope caused by fear. The latter speculation was based on rather flimsy evidence: Eng's bladder was distended and his right testicle retracted. A postmortem cast of the Siamese Twins, as well as their joined livers removed at autopsy, are on display at the Mutter Museum in Philadelphia.

Unlike the Siamese Twins, who were under P. T. Barnum's control only briefly, William "Zip" Jackson was exhibited by Barnum for the greater part of his 67 years on the stage (1859 to 1926).[9] Zip, considered to be the "dean of freaks," was the most popular "pinhead." He was christened "Zip the What's It" after the Prince of Wales, while viewing him at the American Museum in 1860, exclaimed in astonishment "What is it?" Zip's failure to talk was attributed to Barnum's admonishment about jeopardizing the hoax that he was a new species, captured by explorers on the River Gambia "in a Perfectly Nude State, roving among the trees . . . ." In reality, Zip was a poor American black man with microcephaly and mental retardation.

Perhaps the most famous patient with a neurologic disease was John Merrick, known as the Elephant Man. His story was brilliantly and touchingly recorded in *The Elephant Man and Other Reminiscences* by Frederick Treves,[21] Surgeon-Extraordinary to Queen Victoria. Treves, known for his *Surgical Applied Anatomy* (1883)—which remained the authoritative text on the subject for many decades—was also a brilliant surgeon and teacher and a gifted man of letters.[22] He described his first encounter with the Elephant Man on exhibit at a vacant green grocer's shop in London in 1884:

> The showman pulled back the curtain and revealed a bent figure crouching on a stool and covered by a brown blanket. In front of it, on a tripod, was a large brick heated by a Bunsen burner. Over this the creature was huddled to warm itself. It never moved when the curtain was drawn back. Locked up in an empty shop and lit by the faint blue light of the gas jet, this hunched-up figure was the embodiment of loneliness. It might have been a captive in a cavern or a wizard watching for unholy manifestations in the ghostly flame. Outside the sun was shining and one could hear the footsteps of the passers-by, a tune whistled by a boy and the companionable hum of traffic in the road.

Treves, a lecturer on anatomy at London Hospital Medical College, arranged to examine Merrick at the college. Merrick's body was so deformed that he could not appear in public places unless completely hidden by a disguise consisting of a gigantic cap and long black cloak (Figure 8). Treves noted that his deformity

Figure 8.—John Merrick, on admission to London Hospital (from the *British Medical Journal*, Vol. 2, 1886).

Figure 9.—John Merrick. Shortly before death at London Hospital (from the *British Medical Journal*[20]).

Figure 10.—John Merrick's Skull. (Reproduced with permission of E. P. Dutton, Inc., from Montagu.[22])

concerned the cutaneous and osseous systems and described the increased subcutaneous tissue, multiple "papillomatous growths," and the extensive "bony exostoses" and hypertrophy of limbs.[23] However, it is not surprising that Treves did not recognize this disorder that had been delineated only two years earlier by Frederich von Recklinghausen in his classic monograph on multiple neurofibromatosis.[24] From Treves' description and available photographs, Merrick apparently had extensive plexiform neuromas with the associated overgrowth of surrounding skin and subcutaneous tissue (elephantiasis neuromatosa), cutaneous pedunculated fibromas, hyperostosis, pronounced kyphoscoliosis and elephantic hypertrophy of the extremities. Hip disease was attributed to tuberculosis but more likely represented an associated cystic bony lesion (osteitis fibrosa cystica), sometimes resulting from an intraosseous neurofibroma.[25] His "bronchitis" may have been cystic lung disease reported to be associated with neurofibromatosis. The surgeon related that there was no suggestion of the disease in any of Merrick's relatives, though it is doubtful if he would have recognized the disorder (certainly not a formes frustes). The Elephant Man was extremely intelligent. This latter fact perhaps rendered his life most tragic of all.

After the examination, Merrick was returned to the itinerant showman and his journey continued. In the ensuing two years, the police frequently closed the exhibit to protect the public decency and Merrick eventually found himself no longer of any value. Thus he was turned loose in Belgium after his manager robbed him of his savings. He found his way back to Dr Treves at London Hospital with difficulty because his grotesque appearance caused him to be chased by crowds whenever he appeared in public. Treves arranged to have him admitted to London Hospital, writing "I had been guilty of an irregularity for the hospital was neither a refuge nor a home for incurables. Chronic cases were not accepted, but only those requiring active treatment." At last Merrick had found a home, almost as secure as the blind asylum of which he fantasized.

Figure 11.—John Merrick's Skeleton. (Reproduced with permission of E. P. Dutton, Inc., from Montagu.[22])

In his sanctuary at London Hospital for the next four years, Merrick was transformed into a gentleman under Dr Treves' tutelage. The Elephant Man became famous, receiving visits from the Princess of Wales and other royalty. He became an avid reader, accumulating a large library, and on occasion attended the Drury Lane Theater, after special arrangements were made to secure him a private secluded box. He related that he was "happy every hour of the day." Treves learned that his favorite patient had been given up by his mother as a small child due, no doubt, to his hideous deformity, and at an early age fell into the hands of unscrupulous showmen:

> Here was a man in the heyday of youth who was so vilely deformed that everyone he met confronted him with a look of horror and disgust. He was taken about the country to be exhibited as a monstrosity and an object of loathing. He was shunned like a leper, housed like a wild beast, and got his only view of the world from a peephole in a showman's cart.

Concerning the development of character, Treves notes that despite such a life of degradation and brutality:

> He had passed through fire and had come out unscathed. His troubles ennobled him. He showed himself to be a gentle, affectionate and lovable creature, as amiable as a happy woman, free from any trace of cynicism or resentment, without a grievance and without an unkind word for anyone.

In April 1890 John Merrick was found dead in bed. His head had become so massive that he had to sleep in a sitting position and when he attempted to sleep "like other people" he experienced respiratory compromise (see Figures 9, 10 and 11). At the inquest held at London Hospital, it was concluded that the cause of death was asphyxia with the weight of head compressing the trachea.[26] However, it was noted that he was found lying on his back and there was no disturbance of his bed coverings, thus he may have suffered an atlantoaxial dislocation with sudden spinal cord compression.[22] Treves concludes,

> As a specimen of humanity, Merrick was ignoble and repulsive; but the spirt of Merrick, if it could be seen in the form of the living, would assume the figure of an upstanding and heroic man, smooth browed and clean of limb, and with eyes that flashed undaunted courage.
>
> His tortured journey had come to an end. All the way he, like another, had borne on his back a burden almost too grievous to bear. He had been plunged into the Slough of Despond, but with manly steps had gained the farther shore. He had been made a "spectacle to all men" in the heartless streets of Vanity Fair. He had been ill-treated and reviled and bespattered with the mud of Disdain. He had escaped the clutches of the Giant Despair, and at last had reached the "Place of Deliverance," where his burden loosed from off his shoulders and fell from off his back, so that he saw it no more.

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Information

Using an Unna's Boot in Treating Ligamentous Ankle Injuries

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LIGAMENTOUS INJURIES of the ankle are commonly encountered by primary care physicians and account for 75% of all ankle injuries.[1] These injuries are responsible for considerable patient morbidity. Most patients report inability to bear weight,[2] swelling,[3] traction pain[4] and pressure pain.[2] Possible complications of a sprained ankle include dislocation of peroneal tendons, development of chronic instability, injury to the peroneal nerves and the tarsal tunnel syndrome.[5] It is important to distinguish in the office or emergency department which injuries are severe sprains (complete or third-degree ruptures) that require referral to an orthopedist.

Many different treatment modalities have been proposed for first-degree and second-degree sprains; controversy exists between plaster immobilization and surgical intervention for treatment of third degree sprains.[5,6] For mild and moderate ligamentous injuries, elastic bandage wrap,[7] ice application followed by range-of-motion exercise,[8] taping,[6] hematoma injection with procaine hydrochloride and hyaluronidase,[9] Hexcelite (padded) posterior splint,[10] bulky pressure dressing,[11] Orthoplast splint, air-stirrup splint,[12] joint aspiration and lidocaine hydrochloride (Xylocaine) infiltration[13] have been proposed. Each of these modalities has one or more disadvantages for a busy emergency department (Table 1).

There are very few studies in the literature in which the eventual outcome using the various treatment modalities for ligamentous ankle injuries is discussed. Recovery time in a group of patients with ankle sprains was significantly less in those in whom Xylocaine infiltration was used (4.4 days) than in those without injection (10.7 days). Both groups were treated by means of elevation, ice compression wraps, crutches and early mobilization.[13] In another study, no difference in outcome occurred in patients treated with either an elastic wrap or a plaster splint.[14]

Elastic wraps can be applied quickly and easily. Their cost is low and vascular compromise from overexuberant wrapping is unusual.[7] The wrap, however, provides poor support and treatment is often not taken seriously by the patient, in many cases leading to reinjury.

Ice application and range-of-motion exercises may be desirable for a team athlete with a minor injury. This modality is usually not applicable to sedentary patients who do not have an athletic trainer available who has extensive knowledge of biomechanics and anatomy. Without careful supervision, the potential for reinjury is high.[8]

Taping with adhesive cloth material can provide excellent support but requires skill to apply. Frequent reapplication is necessary due to the material's rapid softening and resultant loss of support. Generally, taping is used in facilities where athletic trainers or therapists are available.[6]

Hematoma aspiration or injection is infrequently used in an emergency department. It requires considerable skill and careful follow-up evaluation. This technique, of course, does not stabilize an injured ankle.[9]

The Hexcelite and air-stirrup splints are very good

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TABLE 1.—*Methods of Treating Ligamentous Ankle Injuries*

Method	*Time of Application (minutes)*	*Skill Required to Apply*	*Potential Associated Complications*	*Support Provided*	*Patient Compliance Required*	*Approximate Patient Cost*	*Mobilization Promoted (ambulation)*
Unna's boot	2	++	+	++	+	$ 5.50	++
Elastic wrap	1	+	+	+	+	$ 4.50	++
Ice application with range-of-motion exercises	1	++	+	0	+++	nil	++
Taping	3-5	+++	++	++	+++	nil	++
Hematoma injection	5	+++	++	0	+	$ 41.00	+++
Hexcelite posterior splint	1-2	+	+	++	+	$ 52.00	++
Bulky pressure dressing	3	++	+	+	+	$ 6.50	++
Air-stirrup splint	1-2	+	+	++	+	$ 32.00	++
Short-leg cast—plaster	10	+++	+++	+++	+	$ 80.00	+
Short-leg cast—fiberglass	10	+++	+++	+++	+	$100.00	++

+=minimal, ++=moderate, +++=maximal.

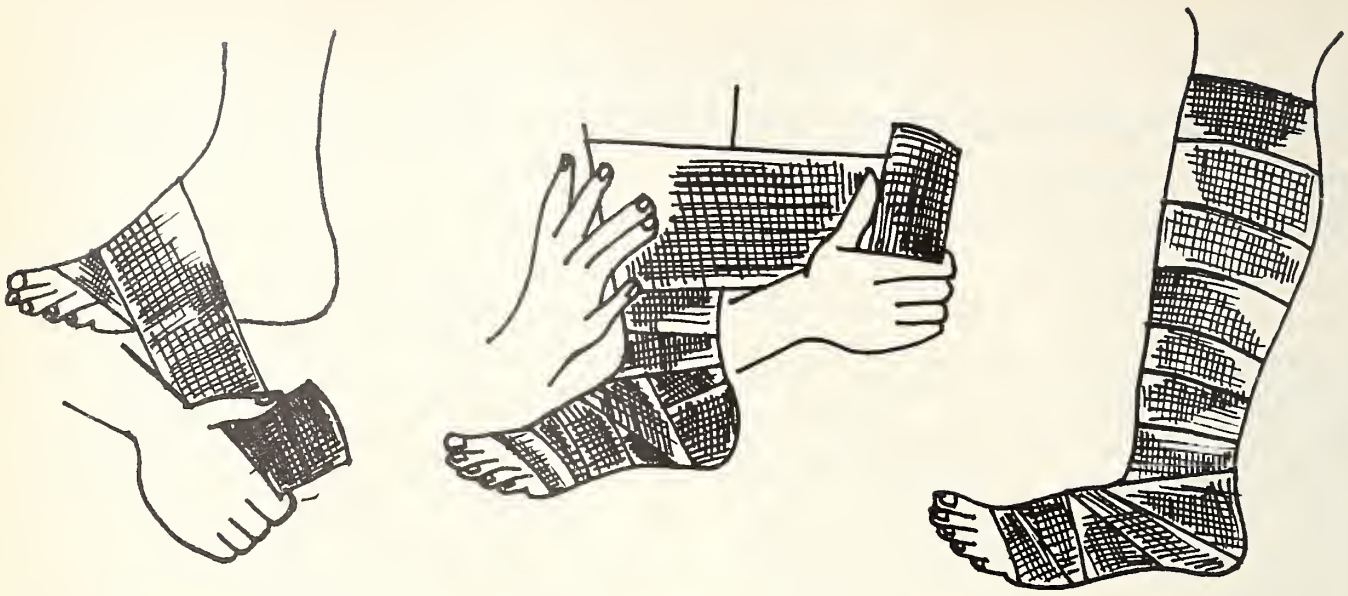

Figure 1.—Application of the Unna's boot. The boot is applied, similar to cast material, from the metatarsal heads to the tibial tubercle.

Figure 2.—The completed application of the Unna's boot. A 10-cm (4-in) elastic rolled bandage is applied over the boot to prevent soiling of garments.

immobilizers of the ankle and are quick and easy to apply. The cost, particularly of the Hexcelite splint, is prohibitive for most hospitals. These splints can be easily removed by patients, often before medically desirable.[12]

A bulky pressure dressing is an easy, safe treatment modality, but for the relatively little support it provides, it is cumbersome for patients. Other than reinjury, there are few potential complications.

A plaster or fiberglass cast is frequently used for severe sprains; it has some limitations for grade I and grade II sprains. Both types of cast ensure excellent support of the ankle. The fiberglass cast enables a patient to walk or even swim but is relatively costly. All casts take time to apply, and a follow-up visit is always required for removal.[11]

The modified Unna's paste boot[11,15] is an ideal outpatient or emergency department treatment for nonsevere ligamentous injuries of the ankle. The Unna's boot is a medicated bandage for leg or arm. One brand, Dome-Paste Bandage (Miles Pharmaceuticals, West Haven, Conn), consists of cotton-gauze mesh impregnated with zinc oxide, calamine and gelatin. The bandage is slightly sticky to the touch and measures 10 cm (4 in) by 9.14 m (360 in). This bandage costs a pharmacy or central supply less than $3.50 and is available without prescription. After 24 to 48 hours the bandage dries to a leathery, not completely hard, consistency. The boot is quickly and easily applied and provides good support with little danger of vascular compromise. It allows patients to bear weight when appropriate and to retain proprioception, an important concern to athletes.[15] The Unna's boot is greatly underused by the medical community and is not recognized as a treatment method by even emergency department personnel. A review of standard orthopedic and emer-

gency care texts[6,9,16-20] finds no mention of the Unna's boot in the treatment of ligamentous ankle injuries.

Technique of Applying

The boot is applied directly from the package in a fashion similar to rolled cast material. Gloves can be worn to protect the hands. A tubular stockinette is applied from the knee joint to the phalanges. The boot is applied directly over the stockinette from the metatarsal heads superiorly to the tibial tubercle (Figure 1). After application, a 10-cm (4-in) rolled elastic bandage may be applied to prevent soiling of garments (Figure 2). Patient instructions can be tailored to individual needs, but generally the bandage is removed two days after edema has disappeared and painless weight-bearing is possible, about seven days in most patients with first- and second-degree sprains. At this point, a rehabilitation program is prescribed, in association with taping or another boot application.[15] An exercise program,[21] tilt board and drills[15] can be prescribed for active or athletic patients.

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Lyme Disease in Northern California

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Lyme disease is a recently described clinical entity with cutaneous, neurologic, articular and cardiac manifestations. Since the original description of the disease in 1977, more than 500 cases have been reported. Although the vast majority of patients have been from the area near Lyme, Connecticut, we have seen four patients from northern California with various aspects of Lyme disease.

This diagnosis should be considered in patients who have traveled to tick regions and who have a distinctive skin lesion (erythema chronicum migrans). Clinical and epidemiologic evidence suggests the disease is transmitted by a tick, Ixodes dammini *in the eastern United States,* Ixodes pacificus *in the West and* Ixodes ricinus *in Europe. The etiologic agent, a new spirochete, may have been recently discovered.*

Steere and Malawista, with co-workers from Yale University, first described an apparently new disease entity in 1977.[1] The disease was characterized by an unusual annular skin lesion of often very large size. This cutaneous manifestation, erythema chronicum migrans, was frequently followed by an oligoarticular arthritis and other systemic manifestations. As the initial reports were clustered geographically around the small town of Lyme, Connecticut, the syndrome was named Lyme arthritis and later Lyme disease. Aside from a few scattered cases,[2] most Lyme disease patients have been reported from the northeastern United States.[3] We are now able to report four cases from northern California with various aspects of Lyme disease.

Reports of Cases

CASE 1. The patient was a 34-year-old married man, a financial analyst living in Mill Valley, California. In August 1977 while at home he noticed a large annular pruritic lesion on his right flank at the site of an insect bite. He did not remember having been bitten by a tick and had not been outside Marin and San Francisco Counties for many months. The skin lesion persisted for a few weeks and cleared gradually without spreading. About two weeks after the appearance of the rash he began to have pain in his lower back radiating into his groin, thighs and right calf. The back pain then ascended into the thoracic and cervical areas of the spine, eventually causing headaches. He also noted pain without swelling in his large joints, particularly the knees, elbows and left hip. Traveling in southern California, he was seen at a San Diego hospital where initial physical examination showed only pain in the midscapular region on forward flexion of his head. Soon after hospital admission, Bell's palsy developed on the left side of his face. Neurologic evaluation resulted in the clinical diagnosis of viral meningitis with Bell's palsy and therapy with dexamethasone, 3 mg a day, was begun.

Initial laboratory studies, including complete blood count and differential, urine analysis, VDRL, SMA-12 chemistry panel, rheumatoid factor, antistreptolysin O titer, antinuclear antibodies, Monospot test, serum protein electrophoresis, tests of stool specimens for ova and parasites, cryoglobulin screen and cytomegalovirus and toxoplasmosis titers, failed to elicit any abnormalities. The sedimentation rate was initially 10 mm per hour and later 30 mm per hour by the Westergren method. Roentgenograms of the chest and cervical spine showed no abnormalities. A bone scan showed some asymmetry of the sacroiliac joints. A lumbar puncture was not done.

He continued to take dexamethasone, 3 mg a day, for about ten days and then therapy was changed to 250 mg three times a day of naproxen, which was gradually tapered. He slowly recovered so that he was back

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Figure 1.—The fading erythema chronicum migrans rash of case 2.

to work by mid-October 1977. When contacted in May 1982 he said that the symptoms had not recurred.

CASE 2. The patient, a 58-year-old San Francisco housewife, was seen in late October 1977 because painful swelling and redness of the left knee had occurred suddenly while she was quietly sitting at home a week before. The right knee was involved within 24 hours and both ankles soon became similarly inflamed. For eight weeks she had had an annular lesion on the right anterior proximal part of her thigh. This had appeared soon after a weekend trip to Plumas County. She did not recall an insect bite.

On physical examination there was a 12 by 5 cm annular macule on the right anteromedial proximal thigh that had an erythematous border with central blanching (Figure 1). Both knees were moderately swollen but without redness. Mild swelling of both ankles was also present. Arthrocentesis was unsuccessful.

Results of the following laboratory studies were normal: complete blood count, erythrocyte sedimentation rate, urine analysis, chemistry panel, rheumatoid factor, antinuclear antibodies, cryoglobulin screen, C3 complement and quantitative IgM. Human leukocyte antigen (HLA) typing was positive for A28, A29, B7, B14, DR1 and DRw6.

The patient was initially treated with naproxen, 250 mg twice a day, but she returned within three days complaining of pain in the left sacroiliac region. Her left ankle was now very swollen and the other joint symptoms had not lessened. Triamcinolone acetonide, 40 mg, was injected intramuscularly in the region of the left sacroiliac tenderness. This provided her less than 72 hours of relief. She was then placed on a regimen of prednisone, 20 mg per day, tapered to zero over the next two weeks. All of her symptoms cleared during corticosteroid therapy.

She was seen in December 1978 with recurrence of pain and swelling in both knees and painless swelling of the ankles. Pain in the left sacroiliac region and the right groin had also appeared. She had had no recurrence of the skin lesions. Results of a complete blood count, erythrocyte sedimentation rate study, analysis of urine and rheumatoid factor, antinuclear antibody and cryoglobulin tests were normal. C3 complement was elevated at 172 mg per dl (normal, 72 to 134). The symptoms remitted spontaneously in a few days. An episode of knee pain without swelling occurred in December 1979. She was last seen in May 1982 for recurrence of moderate pain and mild swelling of the knees and ankles. Her symptoms remitted within ten days with naproxen therapy.

CASE 3. A 35-year-old man, a dentist, presented in August 1980 for evaluation of a recurrent right knee effusion. In June 1978 a large annular lesion had developed on his trunk several days after a camping trip in the Sierra Nevada mountains. He was seen by a dermatologist who felt he may have sustained a bruise while carrying sacks of cement. He was admitted to hospital in July 1978 because of diffuse myalgias and fever. In addition he had loss of taste on the left side of the tongue and a progressive left facial weakness. Positive physical findings on that admission included a temperature of 39.9°C (103.8°F) with left posterior cervical and axillary adenopathy. A left facial nerve palsy was noted that later spread to the right side. Laboratory studies showed a hematocrit of 39.9% and a leukocyte count of 11,000 per μl, with 73% polymorphonuclear leukocytes, 18% lymphocytes and 9% monocytes. The erythrocyte sedimentation rate was 24 mm an hour. Specimens from three serial lumbar punctures had leukocyte counts ranging from 72 to 124 cells per μl, of which nearly all were lymphocytes. Cerebrospinal fluid protein level ranged from 170 to 216 mg per dl. Cerebrospinal fluid cytologies and viral, bacterial and fungal cultures were negative. Computed tomographic scan of the head was normal. The patient's fever dropped and his neurologic deficit began to improve by the end of his one-week hospital stay. The facial palsies cleared completely within a month but he had persistent cerebrospinal fluid pleocytosis and elevated protein level, which finally resolved completely by May 1979.

In December 1979 pain with effusion developed in his right knee. Synovial fluid analysis showed a leukocyte count of 18,220 cells per μl (81% polymorphonuclear leukocytes), protein level of 4.8 grams per dl and a glucose of 84 mg per dl. The Westergren erythrocyte sedimentation rate was 60 mm an hour. Serum complement (C3) was slightly decreased at 57 mg per dl. Serologic tests for rheumatoid factor, and antinuclear antibodies and a VDRL test were negative. HLA typing was positive for A2, Aw24, B18, Bw51, DR1 and DR5. Because of recurrent effusions and impaired ambulation, the patient received

Figure 2.—Two lesions showing fresh erythema chronicum migrans with central cyanosis (case 4).

Figure 3.—The known distribution of *Ixodes pacificus* in California (from Furman and Loomis[5]).

systemic and intra-articular steroids as well as nonsteroidal antiinflammatory agents. The pain and swelling of the patient's knee gradually abated over a period of 12 months. Aside from a single mild flare of right knee symptoms after vigorous exercise he remained well when last seen in March 1982.

CASE 4. The patient, a 30-year-old married woman, presented in November 1980 for evaluation of a skin rash. She had been to Reno, Nevada, ten days before and had noticed an "insect bite" on the posterior aspect of her left thigh a few days later. This lesion began to enlarge in size two days before her office visit and two similar lesions developed on the left leg. She said she had had no fever or systemic symptoms. On physical examination the patient had three annular erythematous lesions with central cyanosis. The largest of these measured 19 cm in diameter. There was central punctate superficial necrosis in each lesion (Figure 2). The patient was given potassium penicillin V, 250 mg four times a day, for ten days. The lesions cleared completely over the next two weeks and no other manifestations of Lyme disease have developed.

The patient's history is interesting: She has had systemic lupus erythematosus since 1964, producing multisystem involvement that included at various times anemia, thrombocytopenia, proteinuria, hepatomegaly, pericarditis and fallopian tube vasculitis. She has had persistent laboratory abnormalities, including a positive antinuclear antibodies test, elevated erythrocyte sedimentation rate, mild proteinuria, increased anti-DNA antibody titer and hypocomplementemia. These remained constant during the episode of erythema chronicum migrans and there was no clinical evidence of an exacerbation of the lupus.

Discussion

Vector and Etiology

The vector for Lyme disease in the eastern United States is the tick *Ixodes dammini*. A closely related tick, *Ixodes pacificus,* was identified by Naversen and Gardner in association with a case of erythema chronicum migrans from Sonoma County, California.[4]

Ixodes pacificus is one of the most commonly encountered ticks attacking humans in California. In a recent survey by Furman and Loomis,[5] the tick was recorded from 49 of the 59 California counties at ele-

TABLE 1.—*"Lyme Spirochete" Antibody Titers via Indirect Immunofluorescence**

Case	Results of Titer
1	Positive 1:640
2	Positive 1:32
3	Positive 1:80
4	Negative 1:20†

*Titers done by Willy Burgdorfer, PhD, Rocky Mountain Laboratories.
†Patient had erythema chronicum migrans only.

vations from sea level to about 2,100 m (7,000 ft) (Figure 3). The tick does not thrive in hot, arid regions or in the intensely developed agricultural areas of the Great Central Valley, but is most common in humid coastal counties and in coastal mountain ranges. It also occurs in the Sierra Nevada mountains, particularly on the western slopes.

Very recently, a new treponema-like spirochete was isolated from the midgut of *I dammini* ticks collected from Shelter Island, New York, a known endemic focus of Lyme disease.[6] This spirochete was shown to bind immunoglobulin of patients convalescing from Lyme disease. The spirochete has also been found in the midgut of *I pacificus* ticks from Oregon and *Ixodes ricinus* ticks from Switzerland.

Serum specimens from our four patients, along with serum specimens from five controls, were submitted blindly to Willy Burgdorfer, PhD, Rocky Mountain Laboratories, Hamilton, Montana, for an indirect immunofluorescence assay. All controls were negative at a dilution of more than 1:20. The specimens from three of our four patients were reactive (Table 1). It is notable that the nonreactive patient (case 4) had been treated with penicillin within days of appearance of the erythema chronicum migrans lesions. No other aspects of the disease ever developed.

Other Laboratory Findings

Erythrocyte analysis sometimes shows a mild normochromic-normocytic anemia. The leukocyte count is usually normal. The Wintrobe sedimentation rate is often moderately elevated in symptomatic patients, averaging 38 mm per hour.[7]

Results of C3 and C4 complement studies are generally within normal limits. In patients who have active erythema chronicum migrans but who do not have involvement of other systems, C3 and C4 levels may be slightly higher than normal, behaving as acute-phase reactants. Significant complement consumption does not appear to be part of this disease.[7]

Immunoglobulin quantitation (IgA, IgG, IgM) results in values within the normal range. Relative differences have been noted, however. Patients with active erythema chronicum migrans in whom joint or nervous system involvement later develops have relatively higher IgM and lower IgG and IgA levels than patients who have only skin involvement. In remission, IgM level falls and IgG and IgA levels rise.[8]

Serum cryoglobulins are found in mildly abnormal amounts in most patients in whom extracutaneous manifestations of the disease later develop. The cryoglobulins in these patients are highest with the appearance of erythema chronicum migrans and fall rapidly with time. The cryoglobulins may contain mixtures of immunoglobulins and complement but are mainly comprised of IgM; 55% contain only IgM.[8]

All synovial fluids contain cryoglobulins. When present in both synovial fluid and serum, the joint fluid cryoglobulins contain a fivefold greater amount of cryoprotein and IgG than serum cryoglobulins, with proportionately less IgM. The joint fluids all show inflammatory reaction, with leukocyte counts ranging from 4,250 to 110,000 cells per μl (median 26,000) with a predominance of neutrophils (median 78%) and an elevated total protein (median 5.6 grams per dl).[7]

The presence of immune complexes as ascertained by abnormal C1q binding is noted in most patients studied. The peak C1q binding activity is present in serum specimens taken during the earliest phase of the illness. It declines rapidly in patients in whom only the skin and joints are affected but persists at 75% of peak levels for months in those patients with cardiac or nervous system involvement. Abnormal C1q binding is present in all synovial fluids and always in higher levels than in the serum.[9]

The B-lymphocyte allele HLA-DR2 was found in seven of ten patients who had chronic erosive arthritis of the knees. It is found in 22% of unaffected persons.[10]

Results of rheumatoid factor, antinuclear antibodies, HLA-B27, uric acid and serum creatinine studies are usually negative or normal.[7]

Clinical Manifestations

These four case histories show the spectrum of Lyme disease. Although not present in every case, the most distinctive feature of Lyme disease is the large, flat, annular lesion of erythema chronicum migrans.[7] This cutaneous lesion may be single or multiple and often reaches very large size with central clearing. A puncture wound from a tick bite is sometimes seen in the center of the expanding lesion. The lesions erupt 4 to 20 days after the tick bite. They are usually on the trunk or proximal extremities and may reach a diameter of 50 cm. Associated symptoms range from none to fever, malaise, sore throat, headache, stiff neck and myalgias. The skin lesion usually fades in a few weeks but may persist for months.

The most frequent complication of Lyme disease is arthritis, which may develop any time from a few days to more than a year after the appearance of the skin lesion. The attacks of arthritis are usually rapid in onset and short in duration but may be recurrent or persist for many months. The knee is most commonly involved and is particularly prone to chronic disease.[10]

A variety of cardiac abnormalities have also been reported in Lyme disease.[11] Symptoms occur a median of 21 days after onset of the erythema. The most common abnormality is a varying degree of atrioventricular

block, including complete heart block. Findings of acute myopericarditis and mild left ventricular dysfunction have also been noted. The duration of cardiac involvement is usually brief.

Nervous system involvement is also seen in some patients with Lyme disease, occurring at the time of the skin lesions or one to six weeks afterwards.[12] Headache, stiff neck and backache are most common. Signs and symptoms of meningoencephalitis and cranial palsy are frequent but chorea, ataxia, radiculoneuritis and myelitis have also been reported. The recovery is usually complete although some patients have residual disability.

Treatment

Recent work suggests that a ten-day course of penicillin or tetracycline given orally bolsters the resolution of erythema chronicum migrans and may prevent the subsequent development of arthritis.[13] The later development of cardiac or neurologic lesions does not appear to be diminished by antibiotic treatment given at that time. Patients with complete heart block have occasionally required a temporary pacemaker.[11] High-dose corticosteroids have been used for severe cardiac[11] or neurologic involvement.[12] Depending on the severity and duration of joint involvement, treatment of the arthritis of Lyme disease may require nonsteroidal anti-inflammatory agents, intra-articular or systemic corticosteroids and, rarely, synovectomy.[10]

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Cowden's Disease: Familial Goiter and Skin Hamartomas

A Report of Three Cases

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Multiple hamartoma syndrome (Cowden's disease) consists of characteristic skin lesions of the face, mucous membranes and distal extremities in association with a variety of benign and malignant internal tumors, especially of the thyroid and breast. We describe a family in which the father, daughter and son were found to have goiter associated with the skin lesions of Cowden's disease. Review of the 40 reported cases of this syndrome indicates that thyroid disease occurs in two thirds of patients with Cowden's disease and most often presents as goiter at an early age. Thyroid cancer has occurred in only three (7.5%) of the patients.

Surgical removal of the large goiter of the son showed that it was composed of multiple encapsulated follicular adenomas and a few areas of lymphocytic thyroiditis. Studies of the thyroid tissue showed that peroxidase activity was decreased, the thyroglobulin had a reduced content of thyroxine and triiodothyronine (perhaps due to the therapeutic suppression of thyroid-stimulating hormone) and thyroxine 5'-monodeiodinase was greatly increased; increased outer ring monodeiodinase activity may be a characteristic of human follicular adenomas.

Cowden's disease is an autosomal dominant disorder diagnosed by characteristic pathologic findings on biopsy of skin lesions.[1-18] The clinical appearance of these skin lesions may be nonspecific, and the diagnosis might not be suspected until other organ system involvement becomes evident. Goiter is frequently an associated disorder. Patients with this disease also have a high incidence of other tumors. Because breast carcinoma and several other malignant diseases occur commonly in this syndrome, the early identification and evaluation of affected patients are of great importance. We report the cases of three members of a family with Cowden's disease and associated large adenomatous goiters.

Reports of Cases

CASE 1. A 62-year-old man, a chiropractor, came to the Veterans Administration-Wadsworth Medical Center in November 1978 because of recurrent goiter. Enlargement of his thyroid was first noted at 28 years of age. At age 35, because of further enlargement, he underwent subtotal thyroidectomy with removal of 90% to 95% of his gland. Each lobe consisted mainly of a single, large, encapsulated adenoma, 3.5 cm in diameter. In 1977 he was found to have recurrent enlargement of the thyroid bilaterally and was treated with desiccated thyroid. Despite this treatment, the thyroid continued to enlarge. Examination showed a diffusely enlarged, smooth goiter without nodules or tenderness; the right lobe was larger than the left. After withdrawal from suppressive therapy, a scan using sodium iodide I 123 showed a patchy distribution of the radioiodine; the 24-hour uptake was 17%. Needle aspiration removed a few drops of hemorrhagic fluid with nondiagnostic cytologic findings. Results of thyroid function tests were normal. Therapy with 0.2 mg of levothyroxine sodium daily was prescribed for sup-

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ABBREVIATIONS USED IN TEXT

T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

pression, and no change in the size of the thyroid gland has been seen during two and a half years.

He has had papular facial skin lesions since his early 20s and sought removal of lesions only when they became large enough to either interfere with his vision or in other ways disturb him cosmetically. He also reported having had palmar warts and numerous lipomas removed. His cheeks, nose and upper eyelids were covered with numerous small papules that were pink, flesh-colored or yellow (Figure 1). His labial mucosa and sublingual areas were covered with yellowish confluent papules in a classical "cobblestone" configuration, similar to that in case 2. His tongue showed pronounced papillomatosis and had a scrotal appearance. A lipoma was present on the left elbow. Histopathologic examination of specimens of three lesions showed two of them to be trichilemmomas and one to be a fibroma.

The patient's father also had characteristic central facial lesions but did not have a goiter.

Case 2. The daughter of the proband, a 33-year-old schoolteacher, was first noted to have goiter at age 22 during her first pregnancy. She underwent subtotal thyroidectomy a year later, with removal of 28 grams of mixed adenomatous tissue. She received thyroid replacement therapy for two years and had normal thyroid function tests in May 1978 after being off therapy for several years. When first seen by us, she had resumed taking desiccated thyroid because of recent enlargement of the right lobe of the thyroid. The thyroid gland was enlarged to about 30 grams. She was placed on a regimen of levothyroxine, 0.2 mg, which effectively suppressed her serum thyroid-stimulating hormone (TSH) concentration to less than 0.3 μU per ml.

She had numerous small papules on her nose and cheeks. She had had dermabrasion for cosmetic improvement of her facial skin, but many lesions that had been removed several years earlier were now recurring.

Figure 1.—Face of patient in case 1, showing characteristic central papules.

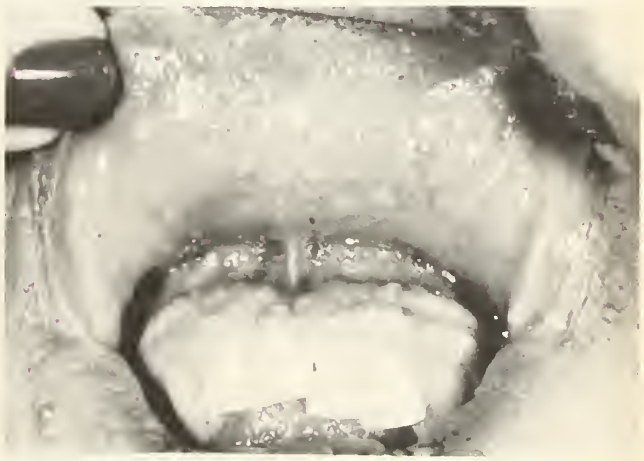

Figure 2.—Cobblestone papules of labial mucosa and gingiva of patient in case 2.

Figure 3.—Pebbly papules of tongue of patient in case 2.

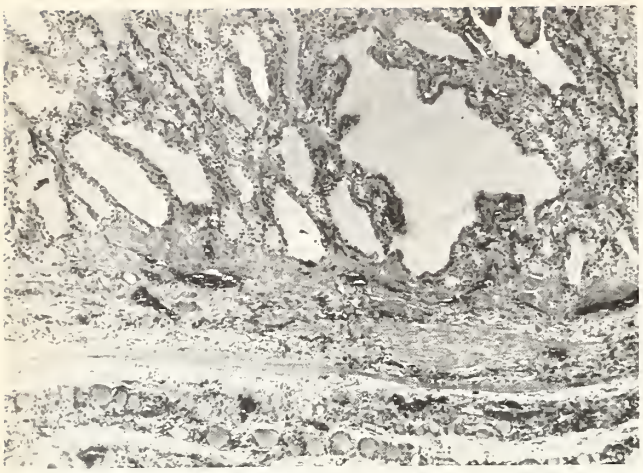

Figure 4.—Thyroid histopathology of specimen from patient in case 3, showing encapsulated follicular adenoma and minimal lymphocytic infiltration.

A basal cell carcinoma had also been removed from her face. She had extensive confluent yellowish papulation of the mucosa of the mouth (Figure 2), and her tongue appeared "pebbly" (Figure 3). She had fibrocystic disease of the breasts.

CASE 3. The 29-year-old son of the proband was first seen in June 1980 for recent enlargement of his neck. He had a large goiter estimated to weigh 80 to 100 grams, with a prominent right lobe and isthmus. Thyroid function values were normal (serum thyroxine [T_4], 6.3 μg per dl; serum triiodothyronine [T_3], 150 ng per dl; serum TSH, 3 μU per ml); however, antimicrosomal antibody titer was positive at 1:6,400, and antithyroglobulin antibody titer was positive at 1:10. Needle aspiration cytology on two occasions yielded only a few tiny aggregates of normal follicular cells. He received thyroxine for suppressive treatment for a year without significant reduction in the size of the thyroid gland. In September 1981 he underwent subtotal thyroidectomy in which 150 grams of tissue was removed.

He had a few papules on his forehead and nose, pronounced cobblestoning of his mucous membranes and a pebbly tongue. A hyperkeratotic firm lesion of his thenar eminence was removed and was found to be a fibroma. In January 1983 he underwent surgical resection of a cerebellar gangliocytoma.

Thyroid Pathology

The thyroid specimen contained multiple nodules and areas of scarring and hyperemia. Microscopic examination showed multiple encapsulated adenomas, poor in colloid and homogeneously solid (Figure 4). There were multiple encapsulated follicular adenomas with follicles of various sizes. Some of the adenomas showed a microfollicular (fetal) growth pattern. There were degenerative changes that included hemorrhage and fibrosis. The glandular tissue adjacent to the adenomas was compressed and contained lymphoid aggregates with germinal centers and groups of Askanazy cells. The histologic findings were consistent with benign follicular adenomas. There was no evidence of invasion of the capsule or of blood vessels.

Review of pathologic material of case 1 showed similar histologic findings.

Biochemical Studies

Thyroid peroxidase activity was measured in the excised thyroid tissue of case 3 by a method recently described.[19] Thyroglobulin was purified by gel filtration of a soluble fraction of thyroid tissue[20]; the T_3 and T_4 content of the Pronase (protease)-digested thyroglobulin was measured by radioimmunoassay. The capacity of this thyroglobulin to form T_4 and T_3 in vitro was assessed by incubation with lactoperoxidase, potassium iodide, diiodotyrosine, glucose and glucose oxidase, followed by digestion with Pronase and measurement of T_4 and T_3 content; baseline hormone content was subtracted.[19] The thyroxine 5′-deiodinase activity of the thyroid tissue was also measured.[21]

Table 1 contains the results of these studies. The T_3 and T_4 content of the patient's thyroglobulin was only 25% and 13%, respectively—that of normal thyroglobulin. This thyroglobulin, however, showed a greater degree of T_3 and T_4 formation in vitro and thus retained adequate capacity to form thyroid hormone. Measurement of thyroid peroxidase activity showed decreased hormone synthesis activity compared with normal thyroid tissue peroxidase. The patient's thyroid 5′-monodeiodinase activity was tenfold greater than normal.

Comments

Multiple hamartoma syndrome was first described in a single patient who had multiple systemic abnormali-

TABLE 1.—*Thyroid Studies of Cowden's Disease*

	Function of Thyroglobulin (Tg)					
	Baseline Content		*Formed Hormone in Vitro*		*Thyroid Peroxidase Hormone Synthesis Activity**	*Thyroid 5′-Deiodinase Production of T_3*
	T_3	T_4	T_3	T_4		
	ng/mg Tg		*ng/mg Tg*		*ng T_4/mg Tg*	*ng T_3/mg enzyme•1 h/ml*
Case 3†	44	222	334	1,680	347	137
Normal thyroid	174±23‡	1,768±265.5‡			443-586‡	13.3±2.3§

T_3=triiodothyronine, T_4=thyroxine

*Hormone synthesis activity is expressed as the amount of newly formed T_4 per 20 μg of thyroid peroxidase.
†All values of case 3 are the mean of duplicate samples.
‡Baseline T_3 and T_4 contents of normal thyroglobulin were the mean ± standard error of the mean (SEM) of 8 normal thyroids. Normal values for thyroid peroxidase and 5′-deiodinase activities were obtained from 4 normal human thyroid glands.
§Mean ±SEM of 4 normal thyroids.

TABLE 2.—*Frequency of Findings in 40 Patients Reported to Have Cowden's Disease**

Location of Lesions	*Out of 40 Cases Reported*
Thyroid	27
Cutaneous (face, acral)	40
Other cutaneous lesions	
Lipomas	15
Hemangiomas	5
Vitiligo	3
Neuromas	2
Oral	33
Scrotal tongue	10
Breast	22
Gastrointestinal	13
Reproductive system	14
Skeletal system	9

*Modified from Thyresson and Doyle.[3]

TABLE 3.—*Thyroid Abnormalities in 40 Patients With Cowden's Disease*

Type of Abnormality	*Patients*
Multinodular goiter	18
Single nodules	5
Carcinoma	4
Thyroiditis	
Subacute	2
Lymphocytic	2
Hypothyroidism	2

ties by Lloyd and Dennis in 1963.[1] This patient had an array of abnormalities that included developmental defects (adenoid facies, hypoplasia of the maxilla and mandible, high arched palate, scoliosis, pectus excavatum), skin lesions with papillomatosis of lips and mucous membranes, scrotal tongue, multiple adenomas of the thyroid that showed some histologic changes indistinguishable from carcinoma, bilateral virginal breast hypertrophy with extensive fibrocystic disease and malignant adenocarcinoma, multiple liver granulomata, bone cysts, low IQ, poor coordination and oligomenorrhea. In 1972 an additional five cases (four women and one man, ages 32 to 41) were reported by Weary and co-workers.[2] All five patients had skin lesions of the face and oral cavity as described by Lloyd and Dennis and, in addition, all had acral skin lesions. Fibrocystic breast disease was present in three of four female patients. All patients had thyroid disease (four had goiter, one had follicular thyroid cancer). Other findings frequently noted included multiple lipomas, adenoid facies, gastrointestinal polyps and cutaneous angiomas. These authors proposed the term *multiple hamartoma syndrome,* and they suggested that the most characteristic finding of the syndrome was the mucocutaneous lesion. Family studies showed autosomal dominant inheritance for this syndrome.

Since these reports an additional 31 cases of Cowden's disease have been reported.[3-17] Reviews of the frequently encountered findings have recently been published by Thyresson and Doyle,[3] Wade[4] and Wade and Kopf.[5] Table 2 lists the most frequent findings in 37 reported cases with the addition of our three cases.

Review of Thyroid Abnormalities

Thyroid disease with onset at an early age is common in patients with Cowden's disease and was present in 68% of 40 cases described (19 women, 8 men). In more than half of these patients, thyroid abnormalities were noted before the age of 25 and in nearly a fourth before the age of 20.

Multinodular goiter was the abnormality of the thyroid most often noted and occurred in 45% of all patients (12 women, 6 men) (Table 3). Two thirds of patients (27) underwent surgical removal of goiter, but there are few reports of the thyroid clinical and pathologic findings. In the original case description, there were several large adenomas with "papillomatosis and adenosis with areas indistinguishable from carcinoma."[1] These changes were similar to those found in the breast lesions of this patient. One autopsy report noted a "colloid and simple nodular goiter."[13] In our case 1, the original pathology was first interpreted as carcinoma, though on our review the lesion was considered benign. Our case 3 showed benign follicular adenomas and lymphocytic thyroiditis.

Solitary nodules were described in five patients. Scans were done on three of these patients; the nodules were "hot" in one patient and "cold" in two. The other two patients were noted to have single nodules on physical examination, and the possibility that these patients had multinodular glands was not further evaluated. One patient with a cold lesion was found to have a follicular adenoma in a gland with diffuse thyroiditis.

Thyroid carcinoma was found in three patients (7.5%)—two follicular, one mixed papillary-follicular—(not including the original case,[1] in which the pathologic description is equivocal). All three patients were women and had coexistent benign breast disease. One of these patients had a sister with thyroid carcinoma. The clinical details of these patients were apparently not available, as all had had a surgical procedure before the cases were reported. Two have required a second operation for locally recurrent disease. No distant metastasis has been reported.

Thyroiditis was diagnosed clinically or pathologically in four patients. In two an episode of rapid painful enlargement of the thyroid gland had occurred. One of these patients had a radioiodine scan showing diffuse reduction in uptake. In a third patient (mentioned above) a cold nodule was found, and surgical pathology showed diffuse thyroiditis with follicular adenoma. Our case 3 also had lymphocytic thyroiditis coexistent with multiple follicular adenomas. Hypothyroidism was diagnosed in only two patients.

The special biochemical studies of the thyroid tissue in our case 3 showed reduced thyroid hormone content of the patient's thyroglobulin but normal capacity of thyroglobulin to form T_4 and T_3, decreased thyroid peroxidase activity and greatly increased 5′-monodeiodinase activity. Suppression of thyroid-stimulating hormone by thyroxine therapy reduces peroxidase activity[22] and could explain the reduced hormone content of thyroglobulin, but it would not explain the increased

5′-monodeiodinase activity because this enzyme is activated by thyroid-stimulating hormone.[23] Recently we have found that human follicular adenomas also contain increased outer ring monodeiodinase activity, which may contribute to preferential secretion of T_3 rather than T_4.[24]

Other Lesions

Facial or acral skin lesions occur in all patients who have Cowden's disease. These include facial papules that are 1- to 4-mm, flesh-colored papular lesions, which may coalesce and give a cobblestone appearance. They occur most often on the central face near the orifices (eyes, nose, mouth) or near the pinna. These lesions may resemble verrucae vulgaris but differ from warts in presentation and distribution. Patients are often treated for warts, but the lesions have a tendency to recur and behave like benign hamartomas. Pathologically they are most often reported as trichilemmomas.[18]

Mucosal papules occur on the palate, gingiva and buccal mucosa. These lesions may also coalesce and give a cobblestone appearance. Pathologically they are fibromas. The tongue may show extensive papules with deep fissuring, giving a pebbly, scrotal tongue appearance (Figure 3).

Acral lesions that appear on the dorsal and volar surface of hands and wrists appear as flat-topped, flesh- or brown-colored papules that pathologically are benign keratoses.

Both fibrocystic breast disease and adenocarcinoma of the breast occur frequently in Cowden's disease, affecting 22 of 25 women evaluated. In a review of 21 women with this syndrome by Brownstein and associates,[11] ten had breast cancer (both breasts in four patients). They point out that the median age of women who have Cowden's disease and breast cancer was 46, whereas in patients without cancer the median age was 36, suggesting that the incidence of breast cancer in Cowden's disease may prove to be significantly higher with longer follow-up. One male patient had gynecomastia.

Involvement of the gastrointestinal tract was reported in 13 patients; however, few patients have been extensively evaluated for these lesions. Gastric polyps, colonic diverticula, adenocarcinoma of the colon and leiomyoma of the sigmoid colon have been reported. Whether or not there is a propensity for the gastrointestinal polyps of Cowden's disease to undergo malignant transformation is unknown.

Reproductive system abnormalities have been reported in 14 of 25 women and include functional menstrual irregularities, ovarian cysts, uterine fibroids and uterine leiomyomas; one patient had cancer of the cervix.

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Intestinal Parasites in Immigrant Children From Central America

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To begin to characterize the health needs of the growing number of refugees from Central America, we compiled the results of examinations for ova and parasites of a single stool specimen of each of 128 children of Central American and Mexican background who entered our health center during a four-month period. Among the 96 children who were born in Central America or Mexico, there was a 65% prevalence of parasitic infestation. Pathogens were found in 46% and multiple pathogens in 14%. Among the 32 American-born children there was a 13% prevalence of parasitic infection, but no pathogens were found. There was no correlation between symptoms and the presence of parasites. Screening Central American immigrant children for intestinal parasites is a high-yield procedure and should be part of their routine health care.

Refugees from Central America have been arriving in the United States in substantial and growing numbers over the past few years. A recent estimate by the US Immigration and Naturalization Service placed the total number of Salvadoran refugees alone at more than 500,000, with 200,000 in Los Angeles and 100,000 in San Francisco (April 21, 1982, Immigration and Naturalization Service Memorandum, Central Office, E. B. Duarte, Jr, Director, Outreach Program). Guatemalans and Nicaraguans are also entering the United States in significant numbers. This influx has challenged the health care system to provide medical care that is financially and linguistically accessible and diagnostically and therapeutically appropriate. Though recent literature has described the health needs of the newly arrived Southeast Asian and Cuban immigrants,[1-6] little has been published about Central Americans.

We have begun to characterize the health needs of this population, a group that represents the greatest proportion of patients receiving health care at San Francisco's Mission Neighborhood Health Center. We review the results of screening for intestinal parasites done on children of Central American background seen in a four-month period.

Patients and Methods

Protocol

All Central American and Mexican immigrant children younger than 17 years old who presented to Mission Neighborhood Health Center from December 1981 through March 1982 were screened for parasitic infection by examination of a single stool specimen. At their first appointment we recorded the country of origin, history of prior parasitic infection and presence of gastrointestinal symptoms as well as routine pediatric information. During the same period, 32 children of Central American and Mexican background, born in the United States, were similarly screened. A clinic protocol was developed for management of cases in which parasites were found. It included the following recommendations: The notation "parasites" should be entered on the child's problem list, treatment should follow the recommendations of the *Medical Letter on Drugs and Therapeutics,*[7] screening of other family members should be done and there should be testing for ova and parasites after treatment.

Stool Specimen Examination

Each patient was given a set of wooden applicators and two plastic containers—one containing polyvinyl

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alcohol and the other formalin. The use of fixatives obviated the need for a fresh stool specimen and was felt to be most reliable for our study population.

Each specimen was examined as a wet preparation in saline and after staining with modified D'Antoni's iodine.[8] The specimen was then concentrated using the formalin-ether-sedimentation technique and the sediment examined after staining with Gomori's trichrome stain (modified).[9] The zinc sulfate flotation technique was done when appropriate. A fresh specimen without preservatives was subsequently requested if there was a question of the presence of amoebae that could not be confirmed with the initial specimen.[10]*

*Stool specimens were tested for ova and parasites by the Medical Specialty Laboratory, 2503 Bush Street, San Francisco, CA 94115.

TABLE 1.—*Results of Stool Specimen Examination for Parasites by Patient's Country of Origin*

Country	*Positives/Total Screened (percent)*
El Salvador	33/52 (63)
Mexico	14/18 (78)
Nicaragua	9/19 (47)
Guatemala	5/5 (100)
Honduras	1/1 (100)
Costa Rica	0/1 (0)
TOTAL	62/96 (65)

TABLE 2.—*Distribution of Parasites*

Parasite	*Number*	*Percent of Positives N = 62*
Pathogens		
Trichuris trichiura	22	35
Ascaris lumbricoides	17	27
Giardia lamblia	15	24
Entamoeba histolytica	2	3
Hymenolepis diminuta	1	2
Hymenolepis nana	1	2
Hookworm	1	2
Strongyloides sp	1	2
Non Pathogens		
Endolimax nana	27	44
Entamoeba coli	24	39
Iodamoeba bütschlii	1	2

Data Collection

Results of all stool specimen examinations for ova and parasites during the study period were returned directly to individual clinic providers and filed separately by the health center's clinical laboratory. In early May laboratory records were used to identify charts of all children screened. Charts were reviewed and the following information was recorded: the name, age and country of origin of each child; which symptoms, if any, were present (diarrhea, abdominal pain, malaise, bloating, pallor or other), and the result of the ova and parasite test.

Results

A total of 96 immigrant children and 32 American-born children were screened at Mission Neighborhood Health Center during a four-month period. They ranged in age from 1 to 16 years, with an average age of 8.8. There was an equal number of boys and girls. Table 1 lists the countries of origin for those born in Central America.

Of the 96 immigrant children, 62 (65%) had positive parasite findings. Table 2 gives the distribution of parasites. Of the 62 children, 33 had more than one parasite and 14 had three or more parasites. There was no significant difference in type of parasite found in children from different countries.

Of the 96 children, 44 (46%) had pathogenic parasites. The most common pathogens were *Trichuris trichiura, Ascaris lumbricoides* and *Giardia lamblia.* Thirteen of these children had more than one pathogen; there were two patients with three pathogens. Table 3 shows each pathogen combination.

Of the 32 children born in the United States, only four had parasites, none of which were pathogenic. One child had *Entamoeba coli* and *Endolimax nana,* two had only *E coli* and one had only *E nana.*

Symptoms did not correlate with the presence of parasites, pathogenic or nonpathogenic. In the group of immigrant children, only 13 of the 62 with parasites and 9 of the 44 with pathogens had symptoms. Of the remaining group of 34 children without parasites, 17

TABLE 3.—*Results of Stool Specimen Examination for Ova and Parasites in 13 Patients With Multiple Pathogens*

Pathogen	*Patients*												
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Trichuras trichiura	+	+		+	+		+	+		+	+		
Ascaris lumbricoides							+	+	+	+	+	+	+
Giardia lamblia	+	+	+	+	+	+			+			+	
Hymenolepis diminuta													+
Hymenolepis nana			+										
Entamoeba histolytica						+							
Hookworm				+									
Strongyloides sp	+												
Endolimax nana	+	+	+		+	+	+						
Entamoeba coli	+	+	+					+	+				
Iodamoeba bütschlii		+											

had similar symptoms. In the group of American-born children, none of the four with parasites were symptomatic, whereas 22 of the 28 without parasites had symptoms.

Discussion

It it likely that our findings underestimate the presence of intestinal parasites in immigrant children, as only a single stool specimen was examined for each child, and our patient population may be a somewhat skewed sample of Central American immigrants. Poorer and less educated immigrants, inexperienced in the use of health care systems, may have a tendency to obtain emergency room care only. Central American refugees who reach San Francisco seem to be largely from the working and professional strata of society.

Although organized health screening programs were established for Southeast Asian and Cuban refugees entering the United States, there has been no such program for Central Americans. As a result, little information is available characterizing their health care needs. Because most intestinal parasitic infections have not been designated reportable diseases, the public health system has not provided this information-gathering function.

The prevalence of intestinal parasitic infection shown here, and the lack of correlation with symptomatology, support the validity of routine screening for all children who were born in Central America. The tendency for many of these infections to persist over long periods,[11,12] the potential for development of significant pathology from infections in the pediatric age group[13,14] and the documented risk of transmission to other children[12] are all factors supporting such screening.

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Doxorubicin (Adriamycin) Cardiomyopathy

A Critical Review

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Despite its vast utility in clinical oncology, the use of doxorubicin hydrochloride (Adriamycin) is limited by a potentially fatal cardiomyopathy. The following critical review, which examines the natural course, histopathologic effects, risk factors and monitoring indicators of this toxicity, also analyzes recent research of proposed mechanisms, including free radical formation with depletion of detoxifying enzymes, inhibition of vital enzyme systems and alterations in relative calcium concentrations. Prevention of the adverse reaction has been attempted by using such agents as α-tocopherol, selenium sulfide, coenzyme Q_{10}, sulfhydryl donors, nucleosides and razoxane, and via liposomal carriage and alternative methods of administration.

The immense value of doxorubicin hydrochloride (Adriamycin) in treating a variety of solid and hematologic malignant conditions is unquestioned. Its usefulness is limited, however, by its cardiotoxicity, an adverse effect of the drug that can preclude its use in some patients and limit the duration of its use in many others. During the past seven years, a number of reviews have been published regarding this chronic and often dose-limiting toxicity of doxorubicin, which underscores its significance.[1-6] The deleterious effects of doxorubicin on the heart can be categorized into acute effects and a chronic cardiomyopathy; this review will focus on the latter toxic effect.

The well-known chronic cardiomyopathy of doxorubicin use greatly limits the usefulness of this broad-spectrum antineoplastic agent. With the increased utilization of chemotherapeutic agents as adjuvants to surgical treatment and irradiation, there will be a greater likelihood of more patients receiving cardiotoxic doses of doxorubicin or even dying of this drug-related toxic effect without evidence of malignant disease. With this in mind, the need to identify risk factors, to predict those persons capable of tolerating further doses of the drug and to possibly prevent cardiomyopathy becomes obvious.

Overview

Prevalence

The overall prevalence of doxorubicin cardiomyopathy is 1.7% to 6.8%[6-13] and is highly dependent on total dose.

Time Course

The outstanding clinical feature of this toxic reaction is its insidious onset, followed by a rapidly progressive biventricular failure and death. The time course varies but symptomatic cardiac failure most frequently appears within a week to 2½ months of the final dose of doxorubicin[1,4,6-8,10,12,14-24] and sometimes there is no latency period.[7,12,17,19,20,25] The median latency period has been reported to be between three and eight weeks[6,7,12,14,15] and has been as long as 2½ years.[26] A number of investigators have noted that the severity of congestive heart failure is greater when the latency period is shorter.[3,6,7,15,17,18]

Signs and Symptoms

The signs and symptoms of doxorubicin cardiomyopathy are typical of any biventricular failure; tachycardia, shortness of breath, neck vein distention, gallop rhythms, ankle edema, hepatomegaly, cardiomegaly

Refer to: Saltiel E, McGuire W: Doxorubicin (Adriamycin) cardiomyopathy (Medical Progress). West J Med 1983 Sep; 139:332-341.

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and pleural effusions were the most frequently noted in a series of 88 cases.[12] Other case reports confirm these findings. Minow and co-workers[6] warn that the first symptom may be as nonspecific as a dry cough and they urge that any new symptom consistent with congestive heart failure should be investigated to rule out a cardiac origin because further doses of doxorubicin may lead to progressive ventricular failure.

Prognosis and Natural Course

In early trials of doxorubicin, the onset of congestive heart failure was abrupt and had an exceedingly poor prognosis; fatality was reported in 70% to 80%.[14,25] It is the hope, however, of many who work with the agent that now that doxorubicin cardiomyopathy is a well-known entity, it will be carefully looked for and that medical treatment at an earlier phase will be more successful. Reviewing cases from the literature, one can now find not only nonresponsive cardiomyopathies with rapid death,* but also many cases of doxorubicin cardiomyopathy that were diagnosed and treated early with good results, the patients still living six months to two years later.†

The natural course of doxorubicin cardiomyopathy begins well before congestive heart failure develops. By analyzing endomyocardial biopsy specimens, it has been well established that myocardial damage is an early phenomenon, occurring after as little as 180 mg per sq m of body surface.[32] It appears, however, that little to no functional deterioration occurs until a certain patient-specific critical dose or critical degree of damage is surpassed.[33] If doxorubicin therapy is discontinued after left ventricular deterioration has occurred, the degree of dysfunction remains but is stable.[34] This may persist for years without the development of congestive heart failure.[35]

In summary, subclinical myocardial lesions can be found early during doxorubicin therapy. After a critical point in therapy, function will begin to deteriorate. Following therapy, noninvasive studies of left ventricular function can show one subset of asymptomatic patients with low resting ejection fractions and another group whose ejection fractions are normal at rest but respond abnormally to stress.[35] This ventricular dysfunction appears to persist for at least a few years. Clinical congestive heart failure, if it is diagnosed early and treated aggressively, may respond to medical management. Patients in whom it develops shortly after their last dose of doxorubicin are less likely to respond to treatment and have a poorer prognosis than those who have a relatively longer latency period.

Description of Myocardial Damage

As stated previously, doxorubicin cardiomyopathy is clinically indistinguishable from other biventricular cardiomyopathies. In dogs, long-term administration of doxorubicin leads to a diffuse cardiomyopathy that is most severe in the left ventricle and intraventricular septum, least severe in the right atrium and intermediate in the right ventricle and left atrium.[36] The disseminated nature of the pathologic effects in the myocardium is well established, and atrial lesions similar to those in the ventricles have been documented in mice and rabbits after long-term therapy.[37] Humans may have a greater incidence of left-sided disease, however.[38] The morphologic nature of doxorubicin cardiomyopathy has been reviewed.[39]

Human histopathologic effects have been studied at autopsy[8] and before death by endomyocardial biopsy.[40] Myocardial sections examined microscopically at autopsy define a rather distinctive vacuolar degeneration of cardiac cells with interstitial edema. Inflammatory changes are notably absent in contradistinction to those seen in viral cardiomyopathy. Ultrastructurally, the intracellular vacuoles are due to distention and swelling of the sarcoplasmic reticulum. The incidence and severity of these changes increase as the total dose of doxorubicin increases.[8]

With the advent of endomyocardial biopsy, it has been possible to observe the progression of myocyte damage at various stages of total dose. The lesions are indeed disseminated yet focal, as normal tissue can be found adjacent to damaged tissue. Two main types of myocyte damage are as follows:

- myofibrillar loss of "drop-out"; the mitochondria are small and remain intact;
- vacuolar degeneration; the earliest manifestation is distention of the sarcoplasmic reticulum, with subsequent swelling and coalescing.

Both lesions progress to death of the myocyte, at which point the mitochondria degenerate with swelling and cristolysis. These changes have been noted after the administration of as little as 180 mg per sq m of doxorubicin, and have been entirely absent after doses as high as 400 mg per sq m.[40] Many of the ultrastructural changes, including vacuolization and dilatation of sarcoplasmic reticulum, are nonspecific and occur with other forms of cardiomyopathy.[41]

In general, the same histopathologic changes that occur in humans develop in a number of animal models in studies of short- and long-term therapy. In fact, studies in animals have allowed us to realize that "clinically evident CHF [congestive heart failure] is . . . a late manifestation of steadily accumulating subclinical damage."[42] After early vacuolar degeneration of myocytes, myofibrillar lysis and cell death ensue. Ultrastructurally, sarcoplasmic vacuolization and mitochondrial degeneration can be seen before myofibrillar separation.[43] The most frequently used and best studied animal models are rabbits, rats and mice; monkeys have also been found to have good correlation with humans. Of these, the rabbit is the most fully understood model of chronic toxic reaction.[42] Although rabbits and rats were the first models to be used and

*References 17, 19, 20, 22, 24, 26-28.

†References 10, 11, 17, 20-23, 29-31.

understood, an excellent study in mice has shown that they too can be used as a model for chronic toxic reaction[44] and justifies the use of this model in the simultaneous assessment of toxicity and efficacy.

Risk Factors for Doxorubicin Cardiomyopathy

In an effort to predict which patients are at greater risk for doxorubicin cardiomyopathy, numerous prospective and retrospective studies and case reports have been published, attempting to alert clinicians.

Age

Those 70 years of age or more are thought to be at increased risk. In the retrospective analysis by Von Hoff and associates of 4,018 patients,[12] there was gradually increasing risk with increasing age, but this appeared to be insignificant at total doses below 500 mg per sq m. It is not clear if this risk is independent of underlying coronary artery disease.

Mediastinal Irradiation

Several investigators have found that prior or concurrent mediastinal irradiation is associated with poorer cardiac assessment scores[19,40] and an increased risk of doxorubicin cardiomyopathy.[7,25] In contradistinction, neither Von Hoff nor Minow and their colleagues[12,15] were able to establish in retrospective analyses mediastinal irradiation as an additional risk factor. Although conflicting information can be found on this controversial area, patients who have received or are receiving irradiation to the mediastinum should be observed more carefully for the development of this toxic condition.

Cyclophosphamide

In the study of Ulmer and co-workers,[19] in children receiving multidrug chemotherapy, which included cyclophosphamide as well as doxorubicin, longer preejection periods developed than in those receiving only doxorubicin. The hypothesis that cyclophosphamide may be a risk factor, though frequently mentioned in reviews, has not been confirmed in at least three large-scale studies.[7,12,15] Recently, however, Gottdiener and colleagues[45] found cardiomyopathy to be a frequent complication of high-dose cyclophosphamide therapy, occurring in 28% of patients within three weeks of treatment. Similar findings were recently reported in rats.[46] As higher doses of this alkylating agent are more frequently being incorporated into chemotherapeutic protocols, the risk of adding cyclophosphamide to a regimen containing doxorubicin will have to be reassessed.

Other Drugs

A number of other drugs, including mitomycin,[16,27] vinblastine sulfate,[16] vincristine sulfate,[7,30] dacarbazine (DTIC),[30,47] bleomycin sulfate,[7] etoposide (VP-16),[20] amsacrine (AMSA)[48] and megestrol acetate[26] have been reported to increase the risk of doxorubicin cardiomyopathy. With the exception of that for mitomycin,[27] none of these reports is well documented.

Preexisting Cardiac Disease

Several investigators have noted an association between pretreatment cardiac disease and hypertension and a greater incidence in the development of doxorubicin cardiomyopathy.[7,8,12] Any patient who falls into this category should be considered at risk.

Dosing Regimen

Apparently a weekly regimen is associated with less cardiotoxic reaction than a regimen calling for a dose every three weeks.[12,49,50] This is conceivably due to the higher doses used with the latter, more common regimen. More frequent administration using smaller doses would produce lower plasma concentrations, and a relationship between cardiotoxic reaction and plasma concentrations has recently been suggested.[51] If doxorubicin cardiomyopathy occurs via free radical or superoxide formation, a single large dose would more likely lead to total depletion of glutathione protection and subsequent myofibrillar damage than would several smaller doses. This area certainly deserves further investigation.

Miscellaneous

It has been suggested that liver dysfunction predisposes to doxorubicin cardiomyopathy [30] Because doxorubicin is eliminated by the liver, this suggestion appears likely. The report is poorly documented, however.

Total Dose

By far the greatest and most well-known risk factor for doxorubicin cardiomyopathy is unrestrained use of the drug. Praga and associates[7] noted an elevation in the incidence curve at 450 to 550 mg per sq m. Lefrak and co-workers[9] found the incidence to be 0.3% at total doses below 550 mg per sq m and 30% at above this dose. Von Hoff and colleagues[12] found a sharp increase in the incidence curve at 550 mg per sq m. At this dose the incidence was 7%, whereas at 700 mg per sq m, the incidence was 18%. The most striking example of the dose dependency of doxorubicin cardiomyopathy is a report by Cortes and associates[10] in which in seven of ten patients receiving more than 600 mg per sq m, congestive heart failure developed, whereas in none of the 88 patients receiving less than 600 mg per sq m did it occur.

The risk factors, as well as the natural course of daunorubicin-induced heart failure, are very similar to those of doxorubicin, but have been far less studied. This subject has recently been reviewed.[14] Of note is that children appear to be at greater risk than adults at any given dose.

Because congestive heart failure develops in a few patients at total doses less than 550 mg per sq m and does not develop in many patients receiving doses above this figure, a total dose guideline appears inade-

quate and the need for monitoring for early and subclinical development of cardiomyopathy is obvious.

Monitoring for Doxorubicin Cardiomyopathy

Several noninvasive and invasive techniques to assess cardiac function have been developed, and most of these techniques have been used to study patients receiving doxorubicin. The ideal test would be free of morbidity and would be able to assess cardiac function accurately at subclinical levels, to predict all patients at risk of congestive heart failure developing with further doses of doxorubicin and to identify those patients who could tolerate further doses of doxorubicin without sequelae. Such a test is not yet available. Many tests have claimed good reliability and specificity for predicting doxorubicin cardiomyopathy; none is foolproof, however.

The use of noninvasive techniques to assess cardiac function has been reviewed.[52] These include electrocardiography, systolic time intervals, echocardiography and radionuclide angiography. A detailed description of the mechanisms of these tests is beyond the scope of this paper; however, their possible usefulness for predicting doxorubicin cardiomyopathy is discussed.

Electrocardiography

Minow and co-workers[13] were the first to suggest that electrocardiography (EKG) would be a good monitoring tool in predicting doxorubicin cardiomyopathy. Since then, however, several investigators have noted that the EKG changes—specifically a reduction of QRS amplitude in the anterior leads—occur late in therapy, frequently do not precede clinical onset of congestive heart failure and thus should not be used as predictive tools.[11,17,53]

Systolic Time Intervals

By using the simultaneous recordings of a phonocardiogram, an EKG and a carotid pulse tracer, one can determine the preejection period, the left ventricular ejection time and the ratio of preejection period to left ventricular ejection time, frequently referred to as the systolic time interval. Although examples of pronounced or sustained elevations in systolic time interval preceding the development of congestive heart failure exist,[21,24,31] there appears to be a high incidence of false-positive elevations in this test,[21,24,25,29,31,54] thus limiting its usefulness. In addition, the incidence of false-negative results has been noted to be as high as 33%.[25] Thus, systolic time intervals do not appear to be a valid predictor of doxorubicin cardiomyopathy.

Echocardiography

The use of echocardiography in assessing left ventricular function has recently been reviewed.[55] M-mode measurements are taken along a single axis and are used to approximate the minor hemiaxis of an ellipse in estimating left ventricular dimensions. Hence, one of the limitations of this test is that it assumes uniform wall motion throughout the ventricle. Henderson and Frei[56] state that because doxorubicin cardiomyopathy is diffuse, this would not pose a problem. But if regional wall motion abnormalities exist or develop independently of doxorubicin, interpretation could be difficult. Two-dimensional echocardiograms provide imaging of the left ventricle from base to apex, thus lessening the need to rely on the assumption of uniform motion. Unfortunately, most studies to date have used the M-mode echocardiogram. The major limitation of either test is in obtaining technically adequate studies for interpretation.[55]

The three assessments of left ventricular function most frequently obtained from echocardiograms are the left ventricular fractional shortening (%SF) or change in internal diameter (%SID), the mean velocity of circumferential fiber shortening (V_{cf}), and the ejection fraction (EF). Because many feel that M-mode determinations of ejection fraction may be inaccurate,[55] the fractional shortening is the most frequently reported value. On the other hand, ejection fractions derived from two-dimensional echocardiograms do compare favorably with more advanced tests.[55] Although some investigators question the usefulness of echocardiography in predicting the onset of congestive heart failure associated with doxorubicin cardiomyopathy,[56] several studies have shown serial decrements in fractional shortening or ejection fraction with increasing doses of doxorubicin, preceding the onset of congestive heart failure.[22,28,34]

Normal value of ventricular fractional shortening ranges from 28% to 40% or even 50%,[22,55] and at least two groups of investigators[22,28] recommend serial measurements with discontinuation of therapy when fractional shortening falls to below 20%. It appears that echocardiography, especially with the advent of two-dimensional imaging, has a role in the noninvasive monitoring of patients receiving doxorubicin.

Radionuclide Angiography

The use of radioactive tracers in assessing heart disease in general[57] and of ventricular function specifically[58] has been reviewed. Two approaches are available: The "first pass" technique—which is rapid—and equilibrium blood pool imaging—which allows multiple images and the ability to "gate" or synchronize the images to a simultaneous EKG tracing and establish composite data. The major measurement obtainable from these studies is the ejection fraction. There is no significant difference between the two methods to reproducibly determine ejection fraction.[59] A normal value has been established at greater than 0.50,[31] with an abnormal value arbitrarily chosen to be from less than 0.45[35] to less than 0.50[54]; Alexander and co-workers[31] set a value of less than 0.45 with a drop of at least 0.15 from baseline to describe "moderate cardiomyopathy," whereas an ejection fraction of less than 0.30 was chosen as a marker of "severe cardiomyopathy." Using the above criteria, they administered an additional doxorubicin dose to five patients who had angiographically defined doxorubicin-induced moder-

ate cardiomyopathy[31]; in all five congestive heart failure developed. Thereafter, six other patients with moderate cardiotoxic manifestation based on radionuclide ejection fraction had their doxorubicin therapy discontinued; in none did congestive heart failure develop, nor did they have worsening of their ejection fraction. In addition, 13 patients were given more than 550 mg per sq m, as their ejection fractions were maintained above the requisites of discontinuation; congestive heart failure did not develop in any of these patients. Other examples of the predictive ability of radionuclide angiography have been published as well.[60] From another study,[60] it should be noted that a low baseline ejection fraction (less than 0.45), without signs or a history of cardiovascular disease, does not place a patient at greater risk of doxorubicin cardiomyopathy developing. In these patients, a drop in ejection fraction of greater than or equal to 0.15 should be used as the marker for moderate cardiomyopathy. Tests should always be done before administration of doxorubicin, as abrupt, transient reductions of ejection fraction have been noted 24 to 96 hours after a dose.[61]

Recently, two sets of investigators were able to identify a greater number of patients with abnormal ejection fractions after doxorubicin by stress-testing these patients either by exercise[35] or by administration of methoxamine hydrochloride.[54] With exercise an ejection fraction should rise by at least 0.05. We feel that stress testing has great usefulness in the assessment of doxorubicin cardiomyopathy, especially in borderline cases.

Transvenous Endomyocardial Biopsy

The use of biopsies has also been recommended as a more invasive but more accurate assessment of myocardial damage due to doxorubicin. The history, technique and use of the transvenous procedure were recently reviewed.[62] The usefulness of this test is based on the frequent finding that the histopathologic grade of the biopsy taken from the right ventricle, on a 0 to 3+ scale, correlates favorably with the total dose of doxorubicin.[32,40,63,64] In addition, biopsy grade has also been shown to correlate with evidence for myocardial dysfunction by cardiac catheterization. However, the predictive capabilities obtained from these biopsy results are as yet uncertain. Many patients with grade 3+ biopsy results have catheterization evidence of dysfunction, and in several congestive heart failure will develop.[64] Very few patients with 1+ biopsy results appear to be at risk of congestive heart failure developing. The problem of predictability centers around the patients with 2+ results. In addition, although morbidity has not been a major problem (0.5% to 4.9%),[51,62,63] few centers are capable of doing a transvenous endomyocardial biopsy. It is generally recommended that patients in whom a 2+ biopsy grade develops, even without other evidence of cardiomyopathy, should not receive further doses of doxorubicin.[51,64] This technique may prove very useful in the further understanding of the relationship between structural abnormality and myocardial function. In medical centers in which myocardial biopsies are routinely done, this procedure appears to be the most accurate determinant of cardiomyopathy at subclinical levels.

Recommendations

At institutions where endomyocardial biopsies are not readily available, we presently recommend a baseline (before giving doxorubicin) radionuclide angiographically obtained ejection fraction on every patient scheduled to receive doxorubicin. Thereafter, we stratify patients into those with risk factors and those without risk factors, as per previous discussion. We measure ejection fractions preceding each doxorubicin dose after a cumulative doxorubicin dose of 350 to 400 mg per sq m in the former group, and after 550 mg per sq m in the latter group. Additionally, we recommend stress testing for any questionable or borderline result, and to discontinue therapy if there is not a rise greater than or equal to 0.05 in the ejection fraction with exercise. Other recommendations for discontinuation of therapy follow those of Alexander and coworkers—that is, an ejection fraction of less than 0.45 with a drop of at least 0.15 from baseline.

At institutions where radionuclide angiography is not available, echocardiograms should be substituted, using the above criteria for discontinuation. An M-mode echocardiographic fractional shortening of less than 25% should necessitate discontinuation.

At institutions where endomyocardial biopsies are done, we would use the recommendations of Bristow and Legha and colleagues,[51,65] as follows: The first biopsy should be done after 300 mg per sq m has been given in patients with risk factors, after 420 mg to 480 mg per sq m has been given in patients without risk factors or after noninvasive test results indicate left ventricular dysfunction. Thereafter, biopsy specimens should be obtained every 120 to 240 mg per sq m, and therapy discontinued at a biopsy result of 2+ or 3+.

Postulated Mechanisms of Doxorubicin Cardiomyopathy

As should be clear from the foregoing discussion, a foolproof noninvasive method for predicting which patient's heart is at risk for irreversible insult from additional doses of doxorubicin does not currently exist. Thus, much research effort has been expended in trying to elucidate the specific mechanism or mechanisms by which doxorubicin produces its toxic effect on the heart. Elucidation of a mechanism for cardiotoxicity would make possible (1) analogue synthesis that would theoretically circumvent the toxic effects or (2) development of blocking agents for the toxic manifestations, which would improve the therapeutic index.

Although one mechanism of antitumor activity is felt to be related to DNA intercalation in which subsequent strands break, a second mechanism involving free radical formation has also been described.[66] Whether one or both of these mechanisms is causally related to the cardiotoxicity is as yet unclear. The fol-

lowing discussion will focus on what is known about the mechanisms of doxorubicin cardiomyopathy and some of the research that attempts to abrogate the dose-limiting cardiotoxicity of this agent.

In vitro and in vivo, anthracyclines have been shown to stimulate superoxide production[42,67,68] via a process dependent on the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH).[68] This reaction is thought to be preceded by reduction of the anthracycline to a semiquinone radical, with a subsequent redox reaction with water that produces the superoxide.[42] This electron-flow process, which involves a free radical intermediate, follows Michaelis-Menten kinetics, indicating a saturable protective mechanism.[69] Superoxide radicals are toxic to tissues in and of themselves; in addition, their dismutation to peroxide initiates a radical chain reaction resulting in conversion of unsaturated fatty acids to lipid peroxides, which in turn rapidly decompose to yield, among other products, malondialdehyde.[68] Although unable to detect malondialdehyde in untreated cardiac tissues, Myers and colleagues[68] detected this end-product two to six days after doxorubicin was administered to rats. This rise in malondialdehyde content was also noted by Stuart and associates[70] in human platelet-rich plasma.

Enzymatic protection of cells against oxygen radicals such as superoxides and peroxides consists of glutathione peroxidase, [71] which is dependent on both glutathione and selenium stores,[72] superoxide dismutase[73] and catalase.[67,71] In animal models, cardiac concentrations of these protective enzymes are far lower than those in other organs.[67,73] Doxorubicin produces an acute depression of cardiac glutathione peroxidase,[67] the enzyme that catalyzes the degradation of lipid peroxides and hydrogen peroxide to nontoxic compounds. Thus, by inhibiting the enzymatic degradation of the toxic oxygen radicals for which it is responsible, doxorubicin potentiates its own toxicity. In addition, due to the relatively lower concentrations of detoxifying enzymes in cardiac tissue, the heart would appear to be at greater risk of damage than other organs.

On a related topic, Olson and associates[74] found an acute reduction in the cardiac concentration of reduced glutathione (GSH) after treatment with doxorubicin. Furthermore, pre-doxorubicin depletion of reduced glutathione potentiated the lethality of the anthracycline, indicating that reduced glutathione has a protective role against the effects of doxorubicin on the heart. The exact role of reduced glutathione in the myocardium is not known, but Kosower[75] found a significant role for it in muscle contraction, lending greater credence to a role for its depletion in the development of heart failure due to doxorubicin.

A second postulated mechanism is inhibition of coenzyme Q_{10} (CoQ_{10} or ubiquinone), a coenzyme of mitochondrial succinoxidase and NADH (the reduced form of nicotinamide-adenine dinucleotide) oxidase, which is involved in the electron-transfer process of respiration and coupled phosphorylation.[76] Doxorubicin has been shown to inhibit the functioning of these enzyme systems.[77] The well-known high concentrations of mitochondria in myocardial tissue coupled with the histopathologic findings of alteration of cardiac mitochondria after exposure to doxorubicin lend some credence to this mechanism. A study in rats[78] indicated that doxorubicin's inhibitory effect is due to its binding to the apoenzyme, thus disallowing the binding of the true coenzyme, CoQ_{10}, which it resembles structurally.

A third hypothesis for the mechanism of doxorubicin-induced cardiotoxic reaction is through an increase in intracellular calcium concentrations and calcium transport perturbation. Although high intracellular calcium concentrations have been associated with doxorubicin cardiomyopathy in animal studies,[8] a more recent study showed that disturbed calcium transport is a function of acute but not chronic doxorubicin cardiomyopathy.[79] Thus, it seems unlikely that calcium transport has a key role in the chronic cardiomyopathy seen with anthracyclines. Its role in acute toxic reaction remains to be established. The long-term effect of calcium channel blockers in patients receiving doxorubicin is an area worthy of study.

Other less supported theories on the mechanism of doxorubicin cardiomyopathy include inhibition of sodium-potassium-adenosine triphosphatase,[80] diminution of adenylate charge,[81] inhibition of guanylate cyclase,[82] DNA degradation[83] and inflammation.[84]

Prevention of Doxorubicin Cardiomyopathy

Based to a great extent on the supported theories of the mechanism of doxorubicin's deleterious effects on the heart, numerous investigators have attempted to minimize the degree of injury by using pharmacologic or endogenous substances or other novel approaches.

One of the most intensively studied agents is α-tocopherol, or vitamin E. Among its many pharmacologic and physiologic properties, this vitamin is a scavenger of free radicals, and its deficiency in rabbits or mice produces a myopathy whose histopathologic effects are very similar to those seen in cardiac lesions produced by doxorubicin.[68]

In vitro, vitamin E has been shown to reduce doxorubicin-induced formation of free radicals and malondialdehyde.[70] In animal studies, vitamin E pretreatment has been shown to prevent doxorubicin-induced diminution of reduced glutathione[85] and to reduce the incidence of typical cardiac lesions[86] and of cardiomyopathy.[85] More recently, Van Vleet and Ferrans[87] noted that vitamin E supplementation prolonged survival in doxorubicin-treated rabbits, but only very large doses of the vitamin provided protection from cardiomyopathy. In another study, Van Vleet and co-workers[36] found no benefit of the vitamin in dogs, but the sample size was small. Finally, in a long-term dosing study involving rabbits, Breed and associates[88] found that even very high doses of vitamin E did not have a protective effect on doxorubicin cardiomyopathy. Thus, animal studies have produced mixed results using a large range of doses of vitamin E. The encouraging results, however, of some of the studies, the lack of obvious

toxicity and the observation that the tumoricidal activity of doxorubicin does not appear to be altered have spurred enough interest to initiate studies in humans.

Legha and colleagues[89] administered α-tocopherol in a dose of 2 grams per sq m given orally each day, starting five to seven days before chemotherapy. Doxorubicin in a dose of 50 mg per sq m was administered to 21 patients with breast cancer. The authors noted that plasma levels of α-tocopherol were four to five times greater than baseline, levels that protected rabbits from doxorubicin cardiomyopathy based on Billingham's biopsy criteria. The authors concluded, based on endomyocardial biopsy results, that this dose and schedule of vitamin E did not offer significant protection against cardiotoxic manifestations in humans, but no control group was used. In addition, many of the studies in animals that showed positive results used doses of vitamin E that, when extrapolated to 70 kg of body weight, far exceeded the doses used here. Finally, the duration of vitamin E administration was not stated in the abstract, and may have been inadequate.

Thus many questions exist about the prophylactic use of vitamin E. Although encouraging results have been found in animal studies, the doses and regimens used have varied considerably and indeed may be different from those required in humans. This is an area that will receive much attention in the coming years.

Another nutritional agent, selenium, has received some attention. Selenium is a cofactor for most, if not all, of cardiac glutathione peroxidase[69] and thus plays a role in the detoxification of free radicals. Selenium-containing diets have been associated with a beneficial effect on survival in animals.[69,87] When used in combination with vitamin E, a reduction in doxorubicin cardiomyopathy has been noted,[90] but when used alone no such benefit was found.[87] Although selenium deficiency in other countries has been associated with heart failure, a deficiency of this mineral in this country is rare, and it appears unlikely that selenium will prove beneficial in the prophylaxis of doxorubicin cardiomyopathy.

Based on the hypothesis that doxorubicin inhibits coenzyme Q_{10} and thus interferes with oxidative metabolism in the heart, the administration of this coenzyme in a prophylactic effort has been studied. In vitro, the addition of coenzyme Q_{10} reduces the inhibitory effect of doxorubicin on both succinoxidase and oxidase of the reduced form of nicotinamide-adenine dinucleotide (NADH).[77] Coenzyme Q_{10} given to rabbits[91] or mice[78] has been shown to prevent inhibition of succinoxidase by doxorubicin and has prevented cardiotoxic reactions in these animal systems. Cortes and co-workers[29] gave coenzyme Q_{10} in a dose of 50 mg a day at the start of a doxorubicin-containing protocol to humans in a small noncontrolled study. Of the eight patients observed, only two showed evidence of progressive cardiac dysfunction, as assessed by increasing systolic time intervals. In a previously studied group not receiving coenzyme Q_{10}, eight of ten patients had steadily increasing systolic time intervals with successive doxorubicin doses. Although the use of systolic time intervals in assessing cardiac dysfunction and predicting congestive heart failure in doxorubicin recipients has been criticized, these encouraging results deserve further study.

The findings of doxorubicin-induced depletion of reduced glutathione and the role of the latter in muscle contraction have spurred interest in the use of *N*-acetylcysteine and cysteamine as sulfhydryl substitutes for reduced glutathione in protecting against doxorubicin cardiomyopathy. In the mouse model, use of these agents has prevented a fall in cardiac sulfhydryl concentrations[74] and has been associated with reduced mortality and cardiac lesions,[74,92] without a change in the efficacy of doxorubicin against P-388 ascites tumor. The efficacy of *N*-acetylcysteine was related to dose as well as scheduling (administering before treatment was more effective than concurrent administration or after treatment).[92]

Due to the noted decrease in adenylate charge with doxorubicin, adenosine used in vitro[81] and in mice[93] has been studied. Positive results on cardiac tissue activity and survival have been noted with short-term studies. Intermediate- and long-term studies with assessment of influence on myocardial lesions are lacking but appear worthy of study, based on these encouraging results.

Razoxane (ICRF 159) is an ethylenediaminetetraacetic acid (EDTA) derivative with antineoplastic properties, which may enhance the antitumor activity of doxorubicin.[94] ICRF 187 is the *d*-isomer of razoxane.[95] Animal studies have shown a decrease in mortality when razoxane[96] or its isomer[95] is given before daunorubicin. Protection from cardiac lesions was also noted.[95] The effects against doxorubicin-induced damage, however, appear to be dose-dependent, as low doses are protective but high doses may increase mortality.[96] The reason for the discrepancy in dose requirement of the ICRF cogeners in their protective effects of the two anthracyclines, as well as their mechanism of action, has not been worked out. Due to their tumoricidal activity, however, work in this area is quite interesting, as well as promising.

Two novel approaches in an attempt to decrease the incidence of doxorubicin cardiomyopathy consist of administering the drug by continuous intravenous infusion or encapsulating it within liposomes. Legha and associates[51] administered doxorubicin by continuous infusion into a central vein over 48 to 96 hours to patients with various malignant diseases, and compared their results with matched control patients who received the drug by standard intravenous injection. Although the mean total dose received by the infusion group was significantly greater than by the control group, substantially fewer infusion patients had their doxorubicin therapy discontinued due to severe pathologic changes seen on endomyocardial biopsy. Antitumor effect was not diminished. Peak plasma levels of doxorubicin were substantially lower in the infusion group, possibly indicating lower myocardial concen-

trations. This supposition parallels the finding that smaller doses given weekly are less deleterious than standard doses given every three weeks.[12,49,50] Doxorubicin cardiomyopathy appears to be related to the length of the infusion as a 96-hour infusion was less cardiotoxic than a 24- to 48-hour infusion.[97] With the broadened utilization of ambulatory central catheters (for example, Broviac or Hickman), this mode of administration may have practical implications in the near future.

Rahman and colleagues[98] found that positively charged liposomes retarded the uptake of doxorubicin entrapped in cardiac tissue in mice. In addition, myocytic and myofibrillar structures were well preserved, as compared with controls, and antitumor activity was not altered. These same investigators have more recently extended their findings to a long-term study in mice.[99] Benefit, as measured by posttreatment pathologic grade, was substantial and supports enthusiasm for this idea.

Several other methods of decreasing the cardiotoxic potential of doxorubicin have been studied but have produced less promising results. Included are attempted prophylaxis with digoxin,[23] verapamil,[8,79] antiinflammatory agents,[84] and carnitine, a vitamin essential for the normal oxidation of fatty acids,[100] and the complexation of doxorubicin with a specific antibody,[80] DNA[101] or dextran.[102]

In summary, a variety of methods directed at reducing the cardiotoxicity of doxorubicin have been investigated. The more promising techniques include prophylaxis with vitamin E with or without selenium, coenzyme Q_{10}, *N*-acetylcysteine or cysteamine, adenosine or razoxane and its isomer and administration of doxorubicin by continuous infusion through a central vein or entrapped within liposomes. As several of these techniques are currently undergoing human trials, there is hope that encouraging preclinical data will translate into new clinical methods, allowing greater usage of this important class of antineoplastic drugs.

At a more basic level, the chemical synthesis of doxorubicin analogues that have a greater therapeutic-to-toxic ratio is an avenue continually being pursued. Such a compound—that is, with similar antitumor activity and spectrum as doxorubicin, but lacking or possessing significantly less cardiotoxicity than the parent compound—would be of great use. Although it is not the intent of this paper to review analogue synthesis, a brief discussion of this area follows.

As has previously been mentioned, several good animal models exist for the assessment of anthracycline-induced cardiotoxic reaction, including rabbits, rats and mice. Several investigators have quantified the cardiotoxic potential of various anthracyclines relative to that of doxorubicin using these model systems. Only the mouse model, however, has been shown to be a valid indicator of the therapeutic potential for the anthracyclines. Thus, for a study to fully assess the relative benefit of a novel anthracycline agent as compared with doxorubicin, the dose requirement for a specific tumor cell kill and for specific histopathologic changes in the myocardium due to the agent in question and to doxorubicin must be compared in mice. Unfortunately, very few studies to date have achieved this. This may be due primarily to historical reasons as the rat and rabbit models of cardiotoxic effects were the first to be widely used. As has been discussed, however, mice provide a similarly good model and allow for simultaneous quantification of tumoricidal activity. As an example of the inappropriate use of animal models, mitoxantrone hydrochloride (dihydroxyanthracenedione), which was found devoid of cardiotoxic potential in dogs and monkeys in preclinical trials, was recently shown to be associated with congestive heart failure in 4 of 31 patients treated for breast cancer.[103]

Summary

The usefulness of doxorubicin in the treatment of a variety of malignant disorders is limited by a chronic cardiomyopathy, a frequently fatal toxic reaction that affects 2% to 7% of those given the drug. The cardiomyopathy, which assumes the clinical appearance of a biventricular congestive heart failure, most frequently occurs one to six weeks after the last dose of the drug is administered. Prognosis has been exceptionally poor in the past, with death rates of up to 79% reported, but as the entity is more fully appreciated early treatment can lead to patient recovery. The pathologic change begins well before clinical symptoms. Following discontinuation of therapy, a degree of left ventricular dysfunction apparently persists for years. The pathologic changes of the cardiac lesions are of two major types—myofibrillar drop-out and vacuolar degeneration, with subsequent mitochondrial degeneration. A number of risk factors for doxorubicin cardiomyopathy have been suggested. The most significant is total dose, with the incidence of cardiomyopathy increasing dramatically above 500 mg per sq m. Preexisting cardiac disease and age over 70 years are major risk factors. Other potential risks include mediastinal irradiation, prior cyclophosphamide therapy and, less likely, other drugs, especially mitomycin. Many noninvasive tests are available to monitor for subclinical toxic reaction. Although it is a controversial area, the most promising measurement appears to be the ejection fraction, obtained by two-dimensional echocardiography or radionuclide angiography. Invasively, endomyocardial biopsies may be done and appear to be the best predictor. Among the postulated mechanisms of doxorubicin cardiomyopathy, the most promising include radical formation with lipid peroxidation, depletion of cardiac reduced glutathione, inhibition of cardiac coenzyme Q_{10} and a decrease in cardiac adenylate charge. Finally, a number of measures to protect against cardiomyopathy have been investigated. Of these, the most encouraging are concurrent administration of vitamin E, coenzyme Q_{10}, *N*-acetylcysteine, cysteamine, razoxane (ICRF 159) and its isomer, ICRF 187, and administration of doxorubicin by continuous intravenous infusion or within liposomal carriers. As a

greater understanding of the mechanism of doxorubicin cardiomyopathy unfolds and clinicians utilize noninvasive monitoring, hope exists for reducing the incidence of the crippling toxic effects and for increasing the use of this potentially life-saving chemotherapeutic agent in those patients who need it.

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Specialty Conference

New Advances in Surgical Oncology

Moderator
DONALD L. MORTON, MD

Discussants
FREDERICK R. EILBER, MD; F. KRISTIAN STORM, MD, *and* DAVID H. KERN, PhD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles

Remarkable advances have occurred in surgical oncology, including the development of doxorubicin hydrochloride (Adriamycin) for treating sarcoma. hyperthermia for treating deep-seated tumors by localized magnetic-loop induction and an in vitro assay for cloning human tumor cells. When preoperative administration of doxorubicin, given intraarterially, is followed by irradiation and en bloc resection, it is now possible to preserve the extremities of many patients who have skeletal or soft tissue sarcoma previously treated by amputation. For patients who have advanced cancer in visceral organs, deeply penetrating hyperthermia alone or in combination with irradiation or chemotherapy may destroy active tumor and extend survival. At present, the potential effectiveness of various chemotherapeutic drugs can be tested on clones of a patient's tumor stem cells in vitro, a procedure that may allow us to select the most active drug or combination of drugs for an individual patient.

DONALD L. MORTON, MD:* *We have chosen the following three studies for discussion: extremity preservation, hyperthermia and the clonogenic assay.*

The concept of nonamputative surgical treatment for primary malignant tumors of bone and soft tissues is certainly not new. Initial attempts to resect malignant tumors arising in these sites were largely abandoned in the early 1900s because of the high local recurrence rate.[1] Amputation was then adopted as the only procedure that offered a chance for local disease control.[2]

Early results from radiotherapy trials were also disappointing; these tumors thus gained the reputation of being "radioresistant."[3,4] Interest was rekindled, however, when Suit and associates[5] and Lindberg and colleagues[6] used Fletcher's concepts to show that sarcomas were not radioresistant but were too large and bulky to be treated by irradiation alone. Irradiation could be effective if residual microscopic disease could be eliminated.[6,7]

The discovery of doxorubicin hydrochloride (Adriamycin) in 1973 further modified treatment for both skeletal and soft tissue sarcoma. This antitumor antibiotic was a highly effective chemotherapeutic agent that could induce an overall objective response rate of more than 50% in patients with metastatic disease.[8] Subsequently doxorubicin was administered as an adjuvant after definitive surgical amputation for malignant skeletal and soft tissue sarcoma to eliminate microscopic residual disease in the chest. Several studies indicated that doxorubicin as a single agent, or in combination with other drugs, was highly effective against micrometastatic disease.[9-17]

Hyperthermia is our second subject for discussion. The use of heat in cancer treatment dates back to the ancients, with application of red-hot irons by Ramajama (200 BC), Hippocrates (400 BC) and Galen (200 AD). In 1898 Westermark[18] placed hot-water-circulating cisterns into patients who had advanced carcinoma

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of the uterus and found palliative shedding of some tumors. In 1927 Coley introduced "toxin" therapy for cancer, but stated that responses were associated with temperatures of 39°C to 40°C for several days, suggesting that the febrile reaction might have been the tumoricidal agent.[19] Simultaneously, Keating-Hart and Doyen introduced electrocoagulation of tumors, which is still in use today. Warren in 1932 was one of the first to apply heat from infrared and high-frequency currents to tumors and found remissions of some malignant lesions.[20] With the subsequent development and popularity of x-irradiation therapy, hyperthermia research was all but abandoned until modern times, when the selective thermosensitivity of tumor cells was more fully appreciated.

Last, we shall discuss the clonogenic assay and its current and future uses. Cancer chemotherapy has always been an empiric science. Drugs for an individual patient have been selected on the basis of past statistical response of a particular tumor type. The development of a test predictive of tumor sensitivity to anticancer agents analogous to the bacterial culture for sensitivity has been, understandably, a high priority of cancer research.[21] Early assays, however, did not show a consistent correlation between in vitro activity and clinical response of individual patients. In theory, these early approaches were limited by their failure to identify a critical subpopulation of stem or clonogenic cells.[22] It is now assumed that this unique population of cells has the capability of sustained replication that represents the biologic behavior of a tumor. Based on this principle, Hamburger and Salmon[23] pioneered an in vitro assay in which human tumor stem cells are cloned in agar. This clonogenic assay technology is increasingly used by oncologists as an aid for selecting chemotherapy, by biologists for studying biologic properties of tumor cells and by pharmacologists for evaluating the efficacy of newly developed antineoplastic agents. Recent modifications in technique suggest enhanced growth capacity of tumors and improved predictability of clinical response.

Limb Preservation Procedures for Skeletal and Soft Tissue Sarcomas

FREDERICK R. EILBER, MD:* In 1975 we began a treatment series based on the principles described.[24,25] The protocol called for doxorubicin to be given before radiation therapy and surgical excision. The sequence of therapeutic intervention was based on the premise that treatment of micrometastatic lesions at the periphery of a tumor, given preoperatively (when the blood supply was intact), would enable us to do a local surgical procedure.

From August 1975 until August 1981, a consecutive series of 83 patients with malignant skeletal sarcoma and 100 patients with soft tissue sarcoma was treated. All patients received identical preoperative treatment with intraarterially administered doxorubicin.[26] After percutaneous placement of an intraarterial catheter by the Seldinger technique, catheter location was confirmed by arteriogram. The catheter tip was placed in a high-flow vessel (the common femoral, common iliac or axillary artery). Cutaneous distribution of fluorescein dye was used to monitor proper placement under a Woods lamp daily to confirm the distribution of the continuous drug infusion. Doxorubicin at 30 mg per day was infused continuously through this line during a 24-hour period for each of three consecutive days (for a total of 90 mg). The catheter was then removed and the patients received radiation therapy the following day. A total dose of 3,500 rads was delivered through posteroanterior and anteroposterior parallel opposed ports at a dose fraction of 350 rads per day for at least ten treatments. The entire extremity was treated except for a strip of skin opposite the biopsy site. One to two weeks after preoperative therapy, patients had en bloc resection of all gross tumor. Tumor-free margins were confirmed during the operative procedure by frozen sections.

In patients with skeletal tumors, the affected bone was removed 10 cm proximal to disease as shown by radiographic scan and computed tomography. No major nerves or blood vessels were sacrificed. Operations were done through uninvolved tissue planes. Enneking and co-workers[27] defined these procedures as wide local resections.

Postoperative adjuvant chemotherapy of doxorubicin, 45 mg per sq m delivered for a period of two consecutive days, then, two weeks later, high-dose methotrexate of 200 mg per kg of body weight, was administered to patients with osteosarcoma. This cycle was repeated until a total dose of 450 mg per sq m of doxorubicin was reached. Methotrexate administration was continued once a month for a total treatment time of a year.[25]

Of 75 patients with grade III soft tissue tumors, 35 were treated with chemotherapy (doxorubicin and high-dose methotrexate) and 40 received no adjuvant chemotherapy.

All types of soft tissue sarcoma were classified and staged by the clinical pathologic staging system described by the American Joint Committee on Staging and End Results.[28] One patient had clinical pathologic stage I tumor, 20 had clinical pathologic stage II, 75 had clinical pathologic stage III and four patients were classified as having clinical pathologic stage IV. Clinically, 78 patients had primary disease because they received no previous treatment, 18 had locally recurrent disease after earlier surgical procedures and four patients presented with both intact primary and metastatic disease. The histologic types of primary tumor represented in these patients included 57 with osteosarcoma, 11 with chondrosarcoma, 2 with Ewing's sarcoma, 6 with giant cell tumor and 7 with miscellaneous types of sarcoma that included malignant fibrous histiocytoma

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(3), synovial cell sarcoma (1), leiomyosarcoma (1) and metastatic hypernephroma (1).

After excision of primary skeletal tumors, diseased bone was replaced with a freeze-dried cadaver allograft (National Naval Medical Center, Bethesda, Md) in 23 patients; with a metallic endoprosthesis in 41 patients, and with an intramedullary rod and sliding bone graft in four patients.[29] Of the 15 patients who had no bony replacement, 5 had tumor in the pubis, fibula and radius, and 10 patients had resection of all or a portion of the ilium.[30] Patients were followed at monthly intervals by routine physical examination and roentgenogram of the chest and at three-month intervals by whole lung tomograms.

In this consecutive series of 183 patients, 2 of 83 patients with skeletal sarcoma and 3 of 100 patients with soft tissue sarcoma had disease recurrences (2.7%). Median follow-up time for these patients is 32 months.

Complications of Preoperative Therapy

In 2 of the 183 patients who had preoperative infusions of doxorubicin, arterial thrombosis developed for which they subsequently needed an operative procedure. In one patient, embolectomy (removal of the thrombus) was done and the patient had no further difficulty. In the other patient, complications from the thrombus required amputation of the extremity. No other direct complications related to the infusion of doxorubicin or radiation therapy occurred.

In 13 of the 100 patients with soft tissue tumors, wound slough developed postoperatively, but none required operative intervention. In five patients fracture of adjacent long bones developed and four had lymphedema; the complications that occurred in the rest are as listed in Table 1. All of the fractures of adjacent bone (from which periosteum had been removed at the time of the operative procedure) were in the thigh of patients over 45 years of age. All fractures healed after intramedullary rod fixation. Examination of biopsy specimens at the time of operation confirmed the absence of tumor in the fracture site.

Complications from treatment of skeletal sarcoma largely revolve around the type of bony replacement. The complication rate from allografts was extremely high. Of the original 23 patients who had allografts placed, 6 patients (who had no allograft complications) died 3 to 12 months after their operation for metastatic disease. Of the remaining patients at risk for more than a year, only four have had no complication with the allograft. In all, 13 patients had a serious allograft complication (such as fracture, loosening or resorption and infection) that required additional surgical repair. Four of these patients, or 17%, required amputation, six were treated by allograft excision and replacement with metallic endoprosthesis and in three their allografts were revised. Therefore, of the 23 patients with allografts, 57% required subsequent operative revision. In 41 patients an endoprosthesis was placed and 3 subsequently required operative revision of their prosthesis.

TABLE 1.—*Complications of Treated Patients*

Complications	*Number of Patients N = 24*
Wound slough	13
Fracture of adjacent bone*	5
Lymphedema	4
Fibrosis	1
Pyarthrosis	1
Femoral artery thrombosis	1
Pulmonary embolus	1

*Fractures: 4 in femur, 1 in tibia = 5 of 53 at risk (9%).

TABLE 2.—*Tumor Size in Clinical-Pathologic Stage III Patients Related to Survival*

Tumor Size	*Patients*				
	Studied Number	*Alive Number*	*Percent*	*Follow-up Period Months (range)*	*median*
0-5 cm	18	16	89	(10-54)	33
5-10 cm	34	23	67	(3-84)	31
10-15 cm	23	15	65	(3-72)	25
TOTAL	75	54	72		

Seven of the remaining patients died in less than a year; 29, or 70%, of the total group have been observed for more than 14 months and have not required further surgical intervention.

The overall disease-free survival rate for patients with malignant skeletal sarcoma was compared with a series of patients seen at University of California, Los Angeles (UCLA), who were treated by amputation and the identical adjuvant treatment. There was no statistical difference between the overall survival for patients treated by amputation or by limb salvage. Furthermore, in 2 of the 24 patients who had amputation, local recurrences developed; thus the local recurrence rate was the same for patients treated by amputation or the limb preservation protocol.

The overall survival rate by clinical pathologic stage for patients who had soft tissue sarcoma was 68%. No age group seemed to be at higher risk; this finding, however, may be a statistical phenomenon because patients 10 to 20 years of age have only a 15% survival rate. In Table 2 the size of tumor and overall survival for stage III patients are compared and the size was directly related to overall survival rate.

The purpose of this study was to determine whether or not preoperative therapy with intraarterially given doxorubicin followed by irradiation would be of value for patients with malignant skeletal and soft tissue sarcoma and whether or not these modalities would reduce the incidence of local recurrence after nonamputative operation. It is not yet possible to determine which of the pretreatment methods, intraarterial administration of doxorubicin, radiation therapy or the surgical procedure itself, is responsible for the low recurrence rate or, conversely, the high percentage of primary tumor control in patients who have malignant skeletal and soft tissue sarcoma. The procedure is feasi-

ble, the complication rate is low and the overall ability to save a functional extremity is very high.

Like many studies, this one raises more questions than answers. Is administration of doxorubicin intra-arterially preferable to the intravenous route? As for irradiation, it is not clear whether rapid fractionation has any advantage over standard fractionation and whether the total dose of 3,500 rads is adequate or is excessive. To answer some of these questions, we have started a prospective trial to compare an additional series of patients who have malignant skeletal and soft tissue sarcoma treated by an identical protocol, except for a reduced radiation dose of one half, or 1,750 rads.

Although the exact reason for the improved local control rate is not known because of the multidisciplinary aspect of this trial, it is unlikely that the improvement is related to more adequate surgical procedures. We believe that this local disease control is the result of the multidisciplinary adjuvant therapy that destroys microscopic disease at the periphery of the tumor.

Hyperthermia for Cancer Therapy

F. Kristian Storm, MD:* At temperatures between 41°C and 45°C (106°F to 113°F) cancer cells may be slightly more sensitive to heat than their normal-cell counterparts. In vitro and in vivo tumor models have shown irreversible damage and complete regression of various tumors, whereas normal cells were killed at temperatures at least one degree higher, or more than twice the duration of heating.[31-34]

Heat causes progressive necrosis in tumor cells, but not in stromal or vascular cells within tumors or in normal surrounding tissues.[35] Autolytic disintegration of heat-damaged cells is followed by a pronounced increase in connective tissue stroma and scar formation.[36] This process occurs in tissue cultures of tumor-derived and tumor-producing cells but not in normal and non-tumor-producing cells. When a cell subline derived from a non-tumor-producing line acquires high tumor-producing capacity, it also acquires greater thermosensitivity. Thus, malignant potential, both in vivo and in vitro, is accompanied by decreased thermotolerance.[37,38]

Mechanism of Thermal Kill

Hyperthermia alters DNA and RNA synthesis and depresses cellular enzymatic systems required for cell metabolism and division. Its major mode of action may be to increase plasma and lysosome membrane permeability, causing internal destruction of the cancer cell (Figure 1).

Selective Tumor Heating

Most studies so far have dealt with moderate hyperthermia of 42°C to 43°C alone or combined with x-irradiation or chemotherapy, based on the evidence of selective thermal sensitivity of tumor cells. Lethal temperature-exposure time relations have been established for many cell lines. Several investigators, however, have found that at temperatures approaching 45°C a linear kill takes place due to progressive and irreversible protein denaturation. At such high temperatures the differential susceptibility between malignant and normal cells decreases, and host tolerance becomes the prime consideration.[31,34,37] Therapeutic hyperthermia in this higher temperature range was not thought to be feasible until it was realized that, because of abnormal vascularity and poor blood flow, some solid tumors might act as a heat reservoir. When Shibata and

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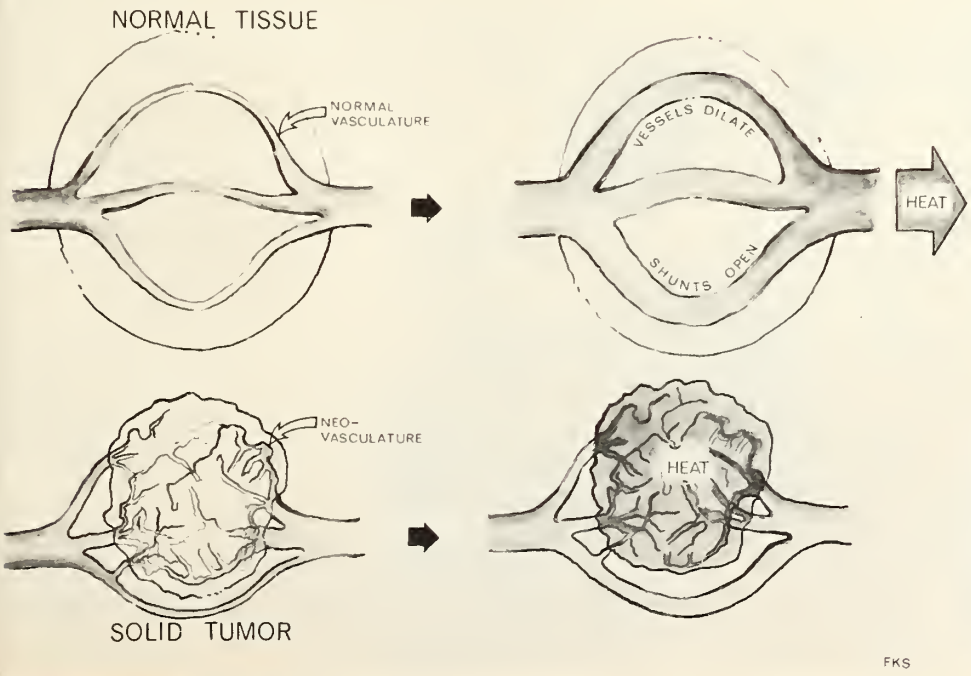

Figure 1.—Postulated mechanism of selective solid tumor heating by radio frequency. Normal tissue blood flow is augmented by heat, not present in solid tumors. Tumors act as relative heat reservoir. (From Storm et al[42]; reprinted by permission of *Cancer Research.*)

MacLean[39] evaluated cancers in humans, they found that the blood supply was poorer in all tumors studied.

Our evaluation of thermal tolerance on animal skin, extremities and viscera supported the safety of temperatures of less than 45°C. When normal animal muscle temperature reaches 43°C to 44°C, spontaneous cooling maintains the tissue well below its thermal tolerance limit. This phenomenon, also observed by others, implies that normal tissue does adapt to hyperthermia in a way that suggests augmented blood flow. When external radio-frequency hyperthermia was applied to normal canine viscera, no selective heating of any normal organ occurred.

Clinical Trials

Isolated limb perfusion. In 1967 Cavaliere and colleagues[34] did regional limb perfusions using prewarmed blood at 42.5°C to 43.5°C in 22 patients with large, recurrent or single metastatic lesions in the extremities. All evidence of gross tumor disappeared in ten patients, five had regressions, three failed to respond and four could not be evaluated. Even though the complication rate was high (six deaths and three immediate amputations), the treatment caused massive tumor necrosis.

Total body hyperthermia. In 1974 Pettigrew and associates[40] reported the cases of 38 patients with terminal cancer treated by total body hyperthermia (immersion in molten wax) at 41.8°C (107.2°F) for an average of four hours. An objective response, weight gain or relief from pain, as well as measured tumor regression or histologic evidence of necrosis, was seen in 18 of 38 patients, though four patients died of disseminated intravascular coagulation.

Larkin and co-workers[41] in 1976 reported their experience with total body hyperthermia applied by a water-circulating suit, maintaining 19 patients at 41.5°C to 42°C for from two to five hours, with an objective tumor response noted in 70%. Complications included one death, transient cardiac arrhythmias in 15%, superficial burns in 15% and transient respiratory distress in 11%, which was attributed to the seven to eight hours of anesthesia time required to raise and maintain body temperatures in these critically ill patients.

Localized hyperthermia. Electromagnetic waves are the most practical means of producing localized hyperthermia. All frequencies heat tissues in a similar way. Energy is transferred into tissue by field interaction; this causes ions in the tissue to oscillate or produce changes in the magnetic orientation of molecules that are locally converted into heat. Because the energy of a shortwave or microwave quantum is only about 10^{-5} eV, it cannot produce ionization or excitation. The biologic effects of these waves are primarily the result of heat production. But the absorption and penetration capabilities of electromagnetic waves depend on tissue composition and interfaces (that is, skin, muscle, fat, bone). Moreover, their depth of penetration is often limited. Incident energy absorption is a function of tissue resistance, so that surface tissues (skin, subcutaneous tissue, body wall musculature) preferentially absorb heat in amounts 10 to 150 times greater than internal organs. Therefore, if superficial tissues must be penetrated to heat deeper tissue, a high and potentially dangerous degree of surface energy deposition would be needed to produce deep heat effectively. In the past, satisfactory heating has been limited to depths of 2 to 3 cm with commercially available apparatus. To overcome this limitation, several investigators designed special equipment to function in the range of 915-MHz and 2,450-MHz microwave bands. Even with surface cooling, however, documented temperatures of 42°C to 44°C have been possible only at 2- to 3-cm

Figure 2.—Circular magnetic-loop induction applicator (20-inch transthoracic and transabdominal electrode shown).

depth, with the thermal gradient continuously decreasing as depth increases.

In 1977 Storm and associates[42,43] introduced magnetic-loop induction hyperthermia for safe thermal treatment of visceral organs (Figure 2). This fundamentally new approach provided potentially therapeutic levels of hyperthermia while sparing surface tissues. With this device (Magnetrode, Henry Medical Electronics, Los Angeles), investigations of the efficacy of localized internal hyperthermia in humans have provided virtually all the available information for response in deep-seated cancers.[44]

Clinical Investigations

Tumor-heating capacity. Of 89 tumors evaluated in skin, subcutaneous tissue or muscle, intra-abdominal viscera, intrathoracic viscera or bone, temperatures at 42°C or more were possible in 69 (78%) tumors, 45°C or more in 32 (36%) and 50°C or more in 22 (25%), while normal tissues remained within a physiologic temperature range of less than 45°C.[43] Of the 89 tumors, 53 were greater than 5 cm in *least* dimension and 36 were at or less than 5 cm. Effective heating at 42°C or higher occurred more frequently in larger tumors (89%) than in smaller tumors (61%).[43]

These reports suggest that potentially effective hyperthermia can be achieved in most superficial and visceral solid human tumors regardless of histopathologic type, though it is most effective for large tumors. Some tumors cannot be safely heated at 42°C or higher and seem to retain their ability to regulate blood flow and dissipate heat. The cooler normal tissue-tumor interface observed in most evaluable cases also suggests that the blood flow at the tumor periphery may have some bearing on the ability to heat tumors effectively.

Histopathologic and gross morphologic effects of heat. In 1971 in Denmark, Overgaard and co-workers[36] treated mouse mammary carcinoma at temperatures of 41.5°C to 43.5°C with localized radio-frequency hyperthermia and found distinct histologic changes in tumor cells but not in stromal or vascular cells within the tumor, or in adjacent normal tissues. They found rapid autolytic disintegration of heat-damaged tumor cells, followed by a pronounced increase in connective stroma associated with progressive scar formation.

In our experience,[44] superficial tumors generally sloughed off, whereas most visceral tumors did not change significantly in size after a transient increase in size during treatment. Serial biopsy specimens showed early coagulation necrosis, edema and vascular thrombosis, then slow replacement of fibrous tissue during many weeks. The vascular thrombosis occurring during hyperthermia slows or prevents the usual mechanisms of resorption. Therefore, a biopsy of the tumor, or careful assessment of tumor-doubling time—that is, stabilization of a previously progressive tumor—is necessary for a determination of the effects of high-temperature on internal tumor therapy. This finding indicates that tumor stabilization may be an important criterion of response to thermal therapy.

Dose response to thermal therapy. To evaluate the thermal death (cell death caused by heat) times of human cancer, we compared the net amount of tumor necrosis in 44 cases of advanced malignancy after electrode-induced hyperthermia at various temperatures and fractionated exposure times.[45] We found that one treatment at 50°C or higher for 17 to 45 minutes resulted in 20% to 100% tumor necrosis, whereas lower temperatures had no apparent effect. Two or three weekly treatments at 45°C to 50°C for 30 to 72 minutes total treatment time produced 70% to 100% necrosis, whereas 40°C to 45°C produced nearly equivalent necrosis but required more than twice the time. Five weekly and ten daily treatments for a total of 135 to 600 minutes produced some tumor necrosis at 40°C to 45°C; for similar amounts of treatment time, however, temperatures above 45°C were the most tumoricidal. Total tumor necrosis by the criterion used (that is, total absence of cell nuclei) was rarely possible even at high temperatures. Although only minimal follow-up was possible in these patients with far advanced cancer. these findings suggested that human tumors might be less responsive to thermal therapy than predicted for by models or induced tumors in animals.

The results of these studies to evaluate hyperthermia as a single agent suggested that higher temperatures, longer treatments and multiple treatments were the most effective. Optimal dose to time regimens and treatment fractionation schedules remain to be determined.

Thermoradiotherapy. Hyperthermia has been combined with radiation therapy in the hope of producing a synergistic and augmented response. Hypoxic cells are more radioresistant than aerobic cells.[46] Gerweck and co-workers[47] have concluded that hypoxic cells may be at least as sensitive to hyperthermia as aerobic cells. Ben-Hur and associates[48] have suggested that the primary effect of hyperthermia is to inhibit cellular recovery from sublethal radiation damage.

When tumor cells were exposed to hyperthermia followed by 600-rad irradiation, the result was a three-log increase in cells killed as compared with their survival at 37°C to 43°C. Clinical doses for local and regional treatment with the combined treatment may lie in the range of 200 to 600 rad per fraction. Recent investigations by Overgaard[49] indicate that hyperthermia is best used three to four hours after irradiation, at 48- to 72-hour intervals.

Thermochemotherapy. The combination of hyperthermia and chemotherapy also has been investigated, because heat is thought to alter the permeability of tumor cell membranes and enhance uptake of chemotherapeutic agents.

In 1970 Giovanella and colleagues[50] found a four-log kill in leukemia cells at 42°C in 3 hours. With the addition of dihydroxybutylaldehyde, a 100-fold kill enhancement was observed with no increase in toxicity. DL-glyceraldehyde, melphalan, sodium oxyamate and actinomycin D (dactinomycin) were also active in com-

bination with heat. In vitro data also suggest benefits from hyperthermia combined with doxorubicin.[51]

In 1977 Goss and Parsons[52] reported on the survival of four human fibroblast strains and seven melanoma cell lines after administering various concentrations of melphalan only and in combination with heat at 42°C for four hours. They found that combined treatment was not only synergistic but increased the differential between fibroblast and melanoma lines.

When Stehlin and associates[53] treated locally recurrent and in-transit melanoma of the extremities using hyperthermic limb perfusion, they found an increased response from 35% to 80% by adding heat (42°C) to melphalan perfusion.

Although few investigations are being done with humans, our recent studies[54] of combined thermochemotherapy for metastatic melanoma in liver are encouraging. Moreover, combined therapy has shown potential benefit and safety of application in animal brain tumors.[55] Clinical trials for refractory human brain malignant lesions are under way at UCLA.

Surgical adjuvant therapy. At temperatures over 45°C, tumors display extensive vascular thrombosis.[42] Thrombosis may not be associated with the number or size of the vessels per se, but rather with the inability of these vessels to augment blood flow in the presence of heat.[43] In selected patients (for example, those who have locally advanced sarcoma) we[56,57] administered high-temperature hyperthermia preoperatively; in some instances, the subsequent resection was facilitated by the avascular nature of the tumor.

Clinical Use of the Clonogenic Assay

David H. Kern, PhD:* The double-layer agar system, called the "human tumor stem cell assay" by its developers, Hamburger and Salmon,[23] was first applied to mutiple myeloma and ovarian carcinoma. Subsequently, a variety of tumor types have been cultured in the clonogenic assay. Using modifications of this original process, the UCLA Division of Surgical Oncology has processed more than 1,000 tumors, of which 62% produced at least 30 colonies in soft agar culture. The major tumor types from which colonies were successfully grown included the following: cancer of the breast, 100 of 140 processed (71%); colon, 102 of 170 (60%); stomach, 29 of 52 (56%); lung, 65 of 85 (76%); ovary, 43 of 57 (75%); soft tissue and skeletal sarcoma, 72 of 120 (60%), and melanoma, 122 of 152 (80%).

To assess the ability of the clonogenic assay to predict clinical responses of patients with solid tumors, Mann and colleagues[58] instituted a prospective, correlative trial. Tumor specimens were obtained from patients with primary and metastatic tumors. Tumor cell suspensions were tested with intravenous formulations of standard chemotherapeutic agents that included doxorubicin, bleomycin sulfate, carmustine, dacarbazine, fluorouracil, methotrexate, mitomycin, melphalan, cisplatin and vinblastine sulfate. Because the alkylating agent cyclophosphamide (Cytoxan) is inactive in vitro, melphalan was used as the standard alkylating agent for in vitro testing; its effects were assumed to be similar to those of cyclophosphamide. Each drug was tested at a dose comparable with the highest concentration pharmacologically achievable in patient serum (Table 3).

TABLE 3.—*Clonogenic Assay: Drugs Tested at Standard Chemotherapeutic Formulations*

Drug	*Concentration μg/ml*
Doxorubicin hydrochloride	0.4
Bleomycin sulfate	2.0
Carmustine	2.0
Dacarbazine	10.0
Fluorouracil	10.0
Methotrexate	4.0
Mitomycin	3.0
Melphalan	1.0
Cisplatin	2.0
Vinblastine sulfate	5.0

Colony growth was assessed three times per week during the course of the investigation using an inverted microscope at × 100 and × 200. Small clusters of cells could be observed within the first week, and colonies (more than 30 cells) were usually apparent in 10 to 14 days. A maximum number of colonies per culture well was reached within three to four weeks, at which time their numbers were recorded and the means and standard deviations for each of the triplicate counts were calculated. Assays were not considered to be evaluable for determination of drug effect unless an average of at least 30 tumor colonies for control plates was observed. To verify the neoplastic validity of the clones, slides of the entire upper agar layer were prepared and stained with hematoxylin-eosin stain and compared with the original histologic findings in the tumor. Special stains, such as periodic acid-Schiff base and silver stains for melanin, were used when appropriate. Mean and standard deviations were calculated for controls and for each individual drug exposure. Antitumor activity of each drug was calculated as the percentage of inhibited colony growth of cells exposed to the drug relative to the number of colonies in the control dishes. In vitro sensitivity to a chemotherapeutic agent was defined as greater than 75% tumor colony inhibition (at the concentration shown in Table 3); less than 75% inhibition of tumor colonies was defined as in vitro resistance.

Responses of patients treated with chemotherapy were classified according to universally accepted clinical criteria. Complete response was defined as disappearance of all clinically apparent disease for longer than a month. Partial response was defined as at least a 50% reduction in the size of all measurable disease for at least a month. Patients whose disease became stable, but who had no objective evidence of tumor regression, were considered nonresponders. Patients received chemotherapy based on the best clinical judgment, independent of the assay result. In vitro assay

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TABLE 4.—*Correlations Between Chemosensitivity as Determined by the Clonogenic Assay and Observed Clinical Responses**

	In Vitro/In Vivo Sensitivity (total correlations = 84)			
	Group 1 (S/S)	*Group 2 (S/R)*	*Group 3 (R/S)*	*Group 4 (R/R)*
Number of patients	21	4	5	54

S = sensitive, R = resistant

*Patients were treated at the UCLA Division of Surgical Oncology and nearby community hospitals.

results were not used to select chemotherapy, but results were later given to the physicians. Responses to chemotherapy were assessed by a patient's oncologist and were later evaluated by independent reviewers. The results of the chemosensitivity testing were compared with the patients' clinical responses to the drug in a blind fashion.

Of 400 patients evaluated to date, 84 had objectively measurable disease and received at least one course of chemotherapy. The correlations between in vitro sensitivity and clinical response are summarized in Table 4.

The clonogenic assay predicted sensitivity for 25 tumors of varying histology; 21 of these 25 patients had evidence of clinical response. For 59 tumors resistant to the drug tested, 54 of these patients showed no response to chemotherapy. Thus, the clonogenic assay was 84% accurate for prediction of sensitivity (21 of 25), and 92% accurate for prediction of resistance (54 of 59). Similar results were obtained by other investigators for selected tumor types.[59,60]

Although good correlations have been found between in vitro chemosensitivity results and clinical responses, several major problems need to be resolved—that is, technical problems and interpretation of results. Technical problems are principally in the areas of tissue disaggregation, drug delivery, culture conditions and colony counting. Scirrhous primary carcinoma of the breast or colon is particularly difficult to dissociate, as is fibrous sarcoma. Although mechanical methods are adequate for most tumor types,[23,59,60] enzymatic dissociation techniques may provide greater cell yield and higher tumor cell viability.[58] Concentrations of anticancer drugs used in the assay vary among laboratories, as do times of exposure of tumor cells to drugs. Nevertheless, comparable results have been obtained from several laboratories, indicating that careful analyses of in vitro data may provide realistic criteria for defining in vitro sensitivity.[58,60]

The commonest tumor types can be cloned by the soft agar technique. It is reasonable, however, to assume that different tumors may have different growth requirements. Culture media and media supplements, such as animal sera, hormones and antibiotics, may need to be specifically tailored for each tumor type. Quantitation of colonies at the completion of the assay is often awkward, time-consuming and somewhat subjective when microscopic counting is used. At UCLA more than 500 assays have been counted using an Omnicon FAS II (Feature Analysis System, Bausch & Lomb, Inc, Rochester, NY). Agreement of machine counts with visual observations has been satisfactory, and the reproducibility of machine counts is excellent.

Even if all technical difficulties of the clonogenic assay are adequately dealt with, the interpretation of results is not a simple task. Perhaps now is the time to ask the question, "How can cancer patients benefit from the clonogenic assay?" Two groups of patients who will not benefit from in vitro chemosensitivity testing are those whose tumors fail to grow in soft agar culture and those whose tumors are most sensitive in vitro to first-line drugs that may be an oncologist's initial choice. There is a third group of patients whose tumors are resistant to all drugs tested. These patients, however, should benefit by being spared the needless side effects of ineffective drugs. Growth rates of tumors in the assay may be increased by improvements in tissue processing and culture conditions. The second group of patients is likely to respond to standard chemotherapy. Moreover, the potential usefulness of the clonogenic assay seems to be limitless.

The clinical response rates of most tumors to chemotherapy show that many tumors are not sensitive to standard or first-line drugs. The clonogenic assay may help identify those patients whose tumors are sensitive to drugs not normally used for a particular tumor type. The assay may be of particular benefit to those patients who had initial responses to drug therapy, but whose disease later recurred or progressed. The clonogenic assay may assist oncologists to select alternative antineoplastic agents for patients who do not respond with their initial courses of therapy. A major application of the clonogenic assay will likely be the rapid screening of new anticancer drugs, so that active drugs can move more rapidly into clinical trials. The availability of the clonogenic assay may influence surgical management of patients.[61] Finally, the selection of patients for treatment with new forms of therapy, such as hyperthermia or thermochemotherapy, may be aided by clonogenic assay results.[62]

The clonogenic assay seems to be applicable to a variety of tumor types. Accurate predictions of chemosensitivity have been obtained for patients with multiple myeloma, sarcoma, melanoma and cancer of breast, ovary, lung, stomach and colon. This assay may have great value for selecting the most efficacious therapy for each patient who has cancer and for alleviating otherwise needless toxic reactions from drugs destined to be ineffective. Large randomized prospective studies will be necessary to determine the overall impact of this predictive test on the treatment of solid tumors. Based on initial encouraging results, these studies are clearly warranted.

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Familial Colonic Cancer Syndromes

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The topic of this conference is inherited colonic cancer syndromes. It will be presented by Dr Richard Boland.*

Dr Boland received his medical degree from Yale and his house-staff training at St Francis Hospital in Hartford, Connecticut. He had further clinical experience in the Indian Health Service and at the Public Health Service Hospital here in San Francisco. After the completion of a fellowship in gastroenterology at the University of California, San Francisco, he joined the faculty as an assistant professor of medicine in gastroenterology at the Veterans Administration Medical Center.

DR BOLAND:† This discussion will focus on the familial colonic cancer syndromes. Cancer of the colon and rectum is very common in the Western countries and can be expected to develop in 5% of the population of the United States. The pathogenesis of most of these cancers is related primarily to environmental factors, since the incidence is highly variable worldwide. Furthermore, in population groups at low risk for the disease such as in Japan, a higher risk develops when they migrate to endemic regions such as North America. Not everyone, however, in any given population group is equally susceptible to the environmental factors responsible for colonic cancer. This malignancy is three to four times more likely to develop in first-degree relatives of patients with cancer of the colon (even excluding those with polyposis coli) than in persons from the general population.[1] At least part of this increased risk may be due to discrete familial cancer syndromes.

There are two general categories into which persons who have the familial colonic cancer syndromes may be divided, those with and those without antecedent polyposis. These two categories may be further subdivided into clinically distinct but closely related syndromes. There is strong experimental evidence that provides a common pathogenetic basis for the polyposis syndromes, and additional lines of investigation that suggest unifying links between some of the polypotic and nonpolypotic colon cancer syndromes, despite the fact that they are clinically quite different. Pertinent case histories will be presented to illuminate these syndromes, followed by a discussion of the clinical features of each and current areas of research.

The Polyposis Syndromes: Familial Polyposis Coli and Gardner's Syndrome

CASE 1. The patient, a 59-year-old man, had crampy lower abdominal pain and intermittently dark feces. He had no history of gastrointestinal disease except that guaiac-positive tests of stool specimens had been noted for many years (in the absence of anemia), which had been attributed to the excessive use of alcohol and aspirin. There was no history in the family of polyps or cancer of the colon. The patient had no children. On physical examination he had several bony protuberances on his skull and occiput that had been present for more than 25 years (Figure 1). He also had several scars due to previous drainage of sebaceous cysts, and had surgical scars from bilateral axillary adenectomy for hidradenitis suppurativa. There were no soft tissue masses, and the abdominal examination elicited no abnormalities. The stool specimen was brown and guaiac test was positive. Other laboratory studies were unrevealing. On sigmoidoscopy there were multiple small polyps in the rectum and sigmoid colon. A barium enema study showed two large masses that nearly obstructed the transverse colon (Figure 2) and multiple smaller colonic polyps. The small polyps were tubular adenomas and the large masses in the transverse

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colon consisted of a villoglandular adenoma and an invasive adenocarcinoma. The patient underwent an exploratory laparotomy and the large lesions were removed; metastatic disease was found in the liver, however. The specimen of resected colon showed multiple adenomatous polyps (Figure 3). A diagnosis of Gardner's syndrome was made, despite the patient's age and the apparently negative family history.

This case exemplifies several important points that should be made about the closely related disorders, familial polyposis coli and Gardner's syndrome (Tables 1 and 2). Familial polyposis coli is a disease in which several thousand adenomatous polyps may eventually carpet the colon (Figure 4) and carcinoma usually develops if the colon is not removed. The appearance of adenomas antedates the appearance of cancer by about 14 years (Table 3), and it is within this latent period that the premalignant disease should be recognized and treated.[4] The disease is inherited as an autosomal dominant characteristic but, as in our patient, in about 20% of cases, there is a negative family history. At least some of the family histories are spuriously negative because denial of the disease is not uncommon in these families.[5]

Gardner's syndrome has all of the features of familial

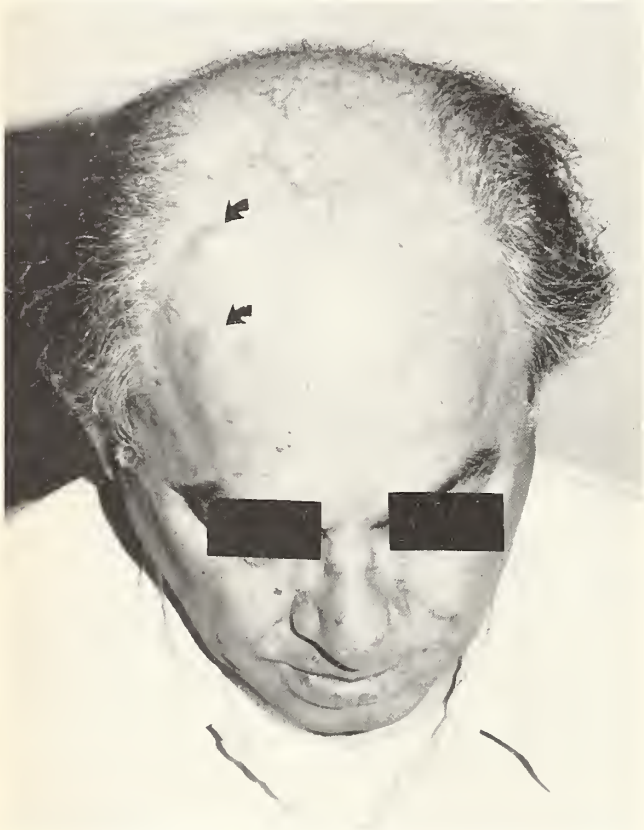

Figure 1.—Arrows show osteomas on the skull of a patient with Gardner's syndrome.

Figure 2.—X-ray film taken during a barium enema study of the patient in Figure 1, showing two large filling defects, numbered (1) and (2) in the transverse colon.

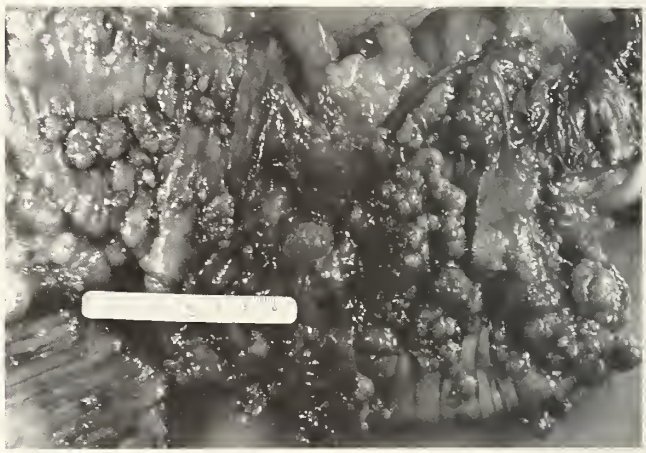

Figure 3.—Resected specimen of ascending colon from the patient in Figures 1 and 2, who had Gardner's syndrome. The specimen shows diffuse colonic polyposis. Most of the polyps were smaller than 5 mm and all were adenomas.

TABLE 1.—*Familial Polyposis Coli*

Characteristic Features
Multiple adenomatous polyps of the colon (up to several thousands)
Autosomal dominant inheritance (20% have negative family histories)
In virtually all colonic cancer develops without colectomy
Polyposis usually begins after puberty; carcinoma typically appears 1 to 2 decades later
Polyps may occasionally occur in the stomach and small intestine (but cancer in these areas is rare)

TABLE 2.—*Gardner's Syndrome*

Characteristic Features
Colonic adenoma and carcinoma similar to that seen in familial polyposis coli
Adenomatous polyps of the small intestine and stomach (other non-neoplastic polypoid lesions are also found in the stomach)
Osteomas, especially of the mandible and cranium
Soft tissue tumors: fibromas, lipomas, sebaceous cysts, epidermoid cysts
Mesenteric fibromatosis (desmoid tumors); may be massive after laparotomy[2]
Dental abnormalities (impacted and supernumerary teeth)
Small intestinal carcinoma (especially periampullary)
Abnormalities of retinal epithelium[3]
Rarely, malignant degeneration of osteomas or soft tissue tumors

polyposis coli, with the addition of a variety of benign soft tissue and bony tumors (Table 2). Patients who have Gardner's syndrome are also at risk for adenomatous polyps and carcinoma of the small intestine, especially in the periampullary region. Polyps are found in the stomach in both syndromes. The gastric lesions have included both adenomas and hamartomatous polyps.[6] To date, cases of gastric carcinoma have been reported in this setting only from Japan, where the general population has a very high incidence of gastric cancer.[7] A number of dental lesions are found in patients with Gardner's syndrome, including mandibular osteomas and impacted or supernumerary teeth. Even when not clinically apparent, a roentgenogram of the mandible will show characteristic lesions in more than 90% of patients.[8] A potentially serious complication is the development of diffuse mesenteric fibromatosis (desmoid tumors) after laparotomy, which can cause gastrointestinal obstruction and prevent additional operative intervention. Mesenteric fibromatosis complicates about 17% of cases of Gardner's syndrome and may occur spontaneously.[2]

In rare instances, osteosarcoma or fibrosarcoma[9] has occurred. Recently, hypertrophy of retinal pigment epithelium has been reported in some, but not all cases of Gardner's syndrome.[3]

Figure 4.—X-ray film taken during a barium enema study in a patient with familial polyposis coli who had diffuse colonic polyposis showing hundreds of tiny adenomatous polyps.

TABLE 3.—*Natural History of Colonic Polyposis*

Stage	*Mean Age Years*
Appearance of adenomas	24.5
Onset of symptoms	33.0
Diagnosis of adenomas	35.8
Diagnosis of cancer	39.2
Death from cancer	42.0

From Bussey.[4]

TABLE 4.—*Overlap Between Familial Polyposis Coli and Gardner's Syndrome*

Colonic neoplasms (adenomas and carcinomas) develop in a similar time frame in both[4]
Occult mandibular osteomas are found in patients with familial polyposis coli[8]
Gastric and small intestinal polyps are found in patients with familial polyposis coli[6,10,11]
Some affected members in Gardner's syndrome families lack extraintestinal manifestations[12]
Similar abnormalities exist in colonic epithelial cells and cultured skin fibroblasts in both syndromes[13]

Clinical Overlap

The clinical overlap between familial polyposis coli and Gardner's syndrome has led some investigators to suggest that these syndromes may be variable expressions of a single genetic defect (Table 4). Most patients with Gardner's syndrome do not have the full clinical triad of polyposis, soft tissue tumors and bony tumors. In one study of 280 family members at risk for Gardner's syndrome, at least one manifestation of the disease had developed in 126 (45%).[14] Of these, 60% had soft tissue tumors, 32% osteomatosis and 67% colonic polyposis; only 20% had the complete triad. Therefore, only a few patients with Gardner's syndrome have the full spectrum of the syndrome, and the polyposis may be inherited separately from the extraintestinal manifestations.[12] Also, when specifically sought, many typical patients with familial polyposis coli have occult lesions in the mandible,[8] the stomach[6] and the small intestine[10,11] similar to those characteristic of Gardner's syndrome. Finally, both syndromes show similar abnormalities in the regulation of the growth of colonic epithelium and cultured skin cells in vitro (see below).

Glioma-Polyposis Syndrome

A variant of the polyposis syndromes is the glioma-polyposis or Turcot syndrome.[15] Several cases have been reported in which siblings have had colonic adenomatous polyposis and malignant brain tumors. In most of the initial reports, the parents did not have a history of polyposis and the affected persons died of their brain tumors. The authors therefore postulated autosomal recessive inheritance of this syndrome, but none of the patients bore offspring to test this hypothesis. A case has recently been reported in which a

family's glioma-polyposis syndrome was inherited in an autosomal dominant fashion.[16] Furthermore, malignant brain tumors have been reported to occur occasionally in families with familial polyposis and Gardner's syndrome, as well as in those with familial nonpolypotic colonic cancer.[12,17] This has led to the more likely conclusion that the glioma-polyposis syndrome is actually a variant of familial colonic cancer syndromes and not a distinct disorder, though the issue has not been entirely settled.[18]

Management

In patients who have familial polyposis coli or Gardner's syndrome cancer of the colon is likely to develop much earlier than in the general population. Fortunately, polyposis develops 10 to 15 years before carcinoma, so that a colectomy can be done before the disease progresses to metastatic malignancy. Polyposis develops in only 5% to 6% of cases before age 20, and the mean age for the detection of the polyps is about 36 years.[4] Our patient presented at age 59, which led his physicians away from the proper diagnosis. One should keep in mind, however, that about 5% of cases present after age 55. No difference in the age of onset or frequency of neoplasia is seen between men and women. Polyps are smaller and the frequency of cancer is much less in patients discovered during the screening of the relatives of an index case, underscoring the value of diligent family screening.

Once the diagnosis of polyposis is made, virtually all patients should be offered colectomy, either total colectomy with abdominoperineal resection or subtotal colectomy with ileorectal anastomosis. Exceptions include adolescents who have not finished growing (in which case the operation may usually be deferred) or patients with metastatic disease, such as our patient, who require only palliative treatment. A complete colectomy is preferred because in a high proportion of patients carcinoma will develop in the rectal segment when it is left behind.[19] In 20% of cases (or less), polyposis does not involve the rectum. These patients tend to be older (median age 58) and usually have negative family histories, suggesting that this may be a clinically distinct subset of polyposis.[19] In the absence of rectal polyposis, the likelihood of rectal cancer developing later is very low and the more limited surgical approach is appropriate. Among patients who have rectal polyposis, however, one initially sees a reduction in the number of polyps following colectomy and ileorectal anastomosis[14] and it was previously assumed that fulguration of the remaining polyps would be adequate management. However, after 20 or more years of follow-up, invasive rectal cancer has developed in a majority (59%) of these patients.[19] For this reason, in most cases of colonic polyposis a proctectomy should be done in concert with one of the newer continent ileostomies.

Unresolved Problems

Several persistent and unresolved problems continue to frustrate the long-term management of these patients. Fulminant desmoid tumors may occur; therapy of these lesions has been disappointing, though some benefit has been reported both with drugs affecting the turnover of adenosine 3′:5′-cyclic phosphate (theophylline and chlorothiazide) and radiation therapy.[7] Gastric lesions include adenomas and a variety of nonneoplastic lesions. These do not seem to require prophylactic surgical management. Small intestinal lesions are far more troublesome because carcinoma (particularly periampullary) is seen in both syndromes,[10,11,20] surveillance of this region is difficult and a prophylactic operation is unreasonable. A number of polypoid lesions have occurred at ileostomy sites, including lymphoid nodules, adenomas and carcinoma.[21] Finally, diligent screening of the relatives of proband cases and genetic counseling are critical procedures that follow the identification of an index case.

TABLE 5.—*Familial Colonic Cancer Without Polyposis*

Characteristic Features
Colonic cancer at an unusually early age risk begins in the third decade peak risk in the fourth and fifth decades
Multiple primary colonic cancer (synchronous and metachronous)
Autosomal dominant inheritance
Increased tendency for cancer in the proximal colon
Increased frequency of mucoid (colloid) cancer[23]
Discrete polyps, but not polyposis, may precede the cancers

From Lynch et al.[22]

Familial Colonic Cancer Without Antecedent Polyposis

Case 2. Our second patient, a 38-year-old man, had a pulmonary embolus. On physical examination, guaiac-positive stools and a possible rectal mass were noted. A carcinoma at the rectosigmoid junction was reported at sigmoidoscopy and the patient then underwent a successful resection of a Duke's B adenocarcinoma. The family history was that colonic cancer had occurred in 5 of the patient's 11 siblings. Review of the pathologic reports confirmed the diagnosis of cancer in each case. In addition, the patient's father had had colonic cancer and another sibling had had a brain tumor, but pathologic records were unavailable for documentation. The average age for the diagnosis of colon cancer in this family was 39 years. Two of the six documented colonic cancers occurred in the cecum or ascending colon, and the other four were in the distal colon. No family member had colonic polyposis or stigmata of Gardner's syndrome.

The disease illustrated by this family is that of familial colonic cancer in the absence of polyposis (Table 5).[22] The trait is apparently inherited in an autosomal dominant manner in these families. Cancer may occur in the third decade, and the risk rises through the fourth and fifth decades of life. Multiple primary carcinomas may be found at the time of initial diagnosis (synchronous); if part of the colon is not

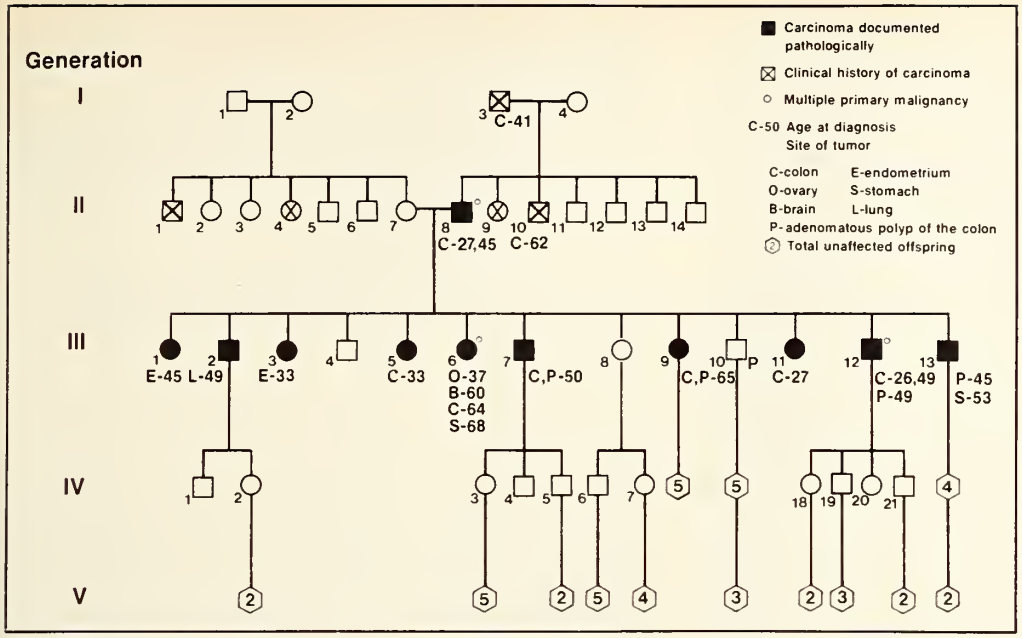

Figure 5.—The family tree from the patient (case 3) with cancer family syndrome. Affected members are found in generations I, II and III; members of generations IV and V are still young.

removed initially, there is a very high likelihood that cancer will recur (metachronous). Recently Lynch[22] has reported an increase in the tendency for cancer to occur in the proximal colon—that is, cecum, ascending or transverse colon—and a rise in the frequency of mucoid or colloid cancer has been reported in this setting.[23] Adenomatous polyps but not diffuse polyposis are often found in the colons of affected persons.

Cancer Family Syndrome

Case 3. The proband, a 49-year-old man, presented with a recurrent colonic carcinoma in the transverse colon 23 years after a cancer had been removed from the cecum (Figure 5, III-12). No fewer than 12 malignant disorders have occurred among 9 of the patient's siblings. Cancer of the colon occurred in the two prior generations. As shown in the pedigree, carcinoma of the endometrium, ovary, stomach, brain and lung has also occurred in this family. Of significance, three additional cases of cancer have appeared (in III-6, III-9 and III-13) since this family was first worked up and the case was reported in 1978.[24] Carcinoma has not been reported in generations IV and V, most of whom are not yet old enough to have reached maximal risk.

The constellation of cases of familial cancer of the colon, female genital tract and other sites has been called "cancer family syndrome" by Lynch, who has reported on several such families.[25,26] These families suffer from all of the cancer risks described in the previous familial colonic cancer syndrome, including early age of onset, multiple primary malignant lesions, colloid cancer and a predilection for cancer of the proximal colon. These patients are at additional risk for adenocarcinoma at other sites throughout the body. The patients do not have antecedent colonic polyposis, but typically may have one or more adenomatous polyps of the colon, as is shown in case 3 (Figure 5). After the colon, the female genital tract (specifically, endometrium and ovary) is at greatest risk for cancer, again occurring one to two decades earlier than that seen in the general population.

Cancer family syndrome has been reported in at least a dozen well-defined kindreds, but is probably more common than currently appreciated. Recognition of the disease is hampered by the absence of any clear marker and the difficulty of making this diagnosis in any small kindred. Lynch has reported the case of one family consisting of 650 members over six generations.[25] The family was first reported on by Warthin in 1913[27] and described in the literature subsequently in 1925,[28] 1936[29] and 1971.[25] The offspring of the affected members of the original sibship continue to be at very high risk for cancer, whereas the descendants of the unaffected siblings have not suffered an unusual incidence of cancer. Colonic cancers have frequently occurred in the third decade in these patients and occasionally in the teens. In the family of case 3, one can find the first incidence of colonic cancer in persons as young as 26 years of age and as old as 65 years, which adds to the burden of surveillance in such families.

Management

Management of the cases of colonic cancer syndrome without polyposis is more difficult than of those with polyposis because there are no markers of premalignant disease. Once the diagnosis is made, one is advised to remove as much of the colon as possible because the entire colon is at very high risk for recurrent tumor. A reasonable compromise in a patient refusing ileostomy is a subtotal colectomy, ileorectal anastomosis and twice-a-year proctoscopy. The risk of an unresectable rectal cancer developing under this management scheme has not been assessed, and it is not possible to predict whether these patients will behave more like those who

have rectal polyposis (who have a poor outcome when the rectum is spared) or like those who do not have rectal polyposis, as discussed previously. Women who are past childbearing age should be advised to undergo removal of the uterus and ovaries at the time of laparotomy. The risk of carcinoma at other sites is not predictable, and prophylactic removal of other organs is not recommended. It is imperative to seek the appropriate relatives for screening when such a person is identified. Offspring of patients who have this disease should begin having periodic surveillance for cancer between the ages of 20 and 25. Testing of stool specimens for occult blood should be done at least once a year (using the standard series of guaiac-impregnated slides, testing two fecal specimens on three consecutive days during which the patient is ingesting a high-fiber, meat-free diet and avoiding drugs such as aspirin, iron or vitamin C, which may produce spurious results). The patients should then undergo a colonoscopy by age 25, to be repeated every two to three years thereafter if negative. If a single adenomatous polyp is encountered, the surveillance should increase to an annual basis. Women should have an annual aspiration cytologic study of the uterus beginning at age 30 as long as childbearing is planned. Surveillance for cancer at other sites relies primarily on careful history taking, physical examination and a high index of suspicion. Lynch and co-workers have emphasized the difficulty encountered when attempting to encourage asymptomatic family members to undergo a diagnostic evaluation because of the problems of fear, complex mythologies concerning cancer and the role of denial in these families.[5]

Other Syndromes

It has recently been reported that typical features of Muir's syndrome (also known as Torre's syndrome), which consists of a group of unusual cutaneous neoplasms (multiple sites of keratoacanthoma, sebaceous adenoma and carcinoma, basal cell and squamous cell carcinoma) in association with a variety of internal neoplasms (including colonic polyps and cancer), have occurred in otherwise representative cases of cancer family syndrome.[30] Because Muir's syndrome is quite rare, the description of a large kindred over several generations or the identification of an objective marker of disease will be necessary to determine whether Muir's syndrome is actually a variant form of cancer family syndrome.

Second, several kindreds, well described in the literature, show an increased incidence of adenomatous polyps (but not polyposis) and colonic cancer. The increased risk for colorectal neoplasia is inherited as if it were an autosomal dominant characteristic with incomplete penetrance.[31,32] The age that polyps and cancer develop, however, is similar to that seen in the general population—that is, not precocious as in the syndromes discussed above—suggesting that the disorder in these families represents a distinct entity.

TABLE 6.—*Increased Tetraploidy in Cultured Skin Cells*

Potentially a marker of certain familial colonic cancer syndromes	
>7% of cultured cells appear to be tetraploid in:	
7/97	control subjects (range, 15%-19% of cells tetraploid)
66/67	Gardner's syndrome patients (range: 9%-35% of cells tetraploid)
5/33	familial polyposis coli patients (range: 8%-14% of cells tetraploid)
0/2	"Glioma-polyposis" patients
5/5	Non-polypotic familial colonic cancer patients
11/26	Offspring of patients with non-polypotic familial colonic cancer

From Danes.[40]

Mechanisms of Disease

In the past five years there has been a dramatic growth of interest in these syndromes. A better understanding of the mechanisms involved in familial colonic cancer will not only illuminate the general problem of carcinogenesis, but may also lead to the identification of premorbid markers of disease. There are still no reliable and easily carried out tests that can be applied to the offspring of such patients to target those who require careful cancer surveillance and to aid in genetic counseling. Several current lines of investigation, however, promise to help in these areas (Table 6).

Aberrant Proliferation of Colonic Epithelium

Deschner has reported abnormal proliferative patterns in the colonic epithelium of patients who have polyposis.[33] In normal colonic mucosa, cell proliferation and new DNA synthesis occur in the lower two thirds of the crypt of Lieberkühn, whereas these processes are repressed in the differentiated cells of the upper colonic crypt. In the flat colonic mucosa of patients who have polyposis, actively proliferating cells may be found in the upper portion of the crypt and in the surface epithelium, indicating a loss of the normal control of growth and proliferation. This lesion may be found at many grossly normal-appearing sites in the colons of polyposis patients and is also found in adenomatous polyps. The earliest neoplastic lesion may be one of inappropriate DNA synthesis and cell proliferation in the upper portion of the colonic crypt, followed in time by the accumulation of these cells and the development of a mass lesion.

Abnormal Growth of Skin Fibroblasts in Culture

Kopelovich and colleagues have reported that cultured skin fibroblasts from patients with familial polyposis coli and Gardner's syndrome display anomalous behavior in monolayer culture.[13] The growth of normal skin fibroblasts is dependent on the presence of serum (typically 15% of the culture medium) and cell density; growth slows or ceases under conditions of reduced serum concentration or at saturation. In contrast, fibroblasts from patients with polyposis continue to grow in 1% serum and do not exhibit normal con-

tact inhibition when confluency is achieved. Additionally, the intracellular actin matrices are abnormal, and the cells synthesize increased amounts of plasminogen activator. These four characteristics are more typical of tumor cells than normal cells, but such fibroblasts do not fulfill the criteria for bona fide malignant transformation because they still require anchorage to a support medium for growth and do not form tumors when injected into nude mice. Kopelovich and associates have shown, however, that these cells are highly susceptible to neoplastic transformation. After exposure to oncogenic virus, fibroblasts from polyposis patients are 100 to 1,000 times more susceptible to transformation than normal cells, and at least partial transformation may be achieved by the addition of tumor promoter to the culture medium.[34] After such "transformation" the cells may grow transiently in soft agar (anchorage-independent growth) and in some cases give rise to tumors when injected into the anterior chamber of the eye of a nude mouse. Other laboratories have confirmed the abnormal growth characteristics and increased susceptibility to viral transformation,[35] and it has been observed that these cells display higher susceptibility to transformation after exposure to alkylating agents.[36,37] Some questions remain, however, concerning the effects of tumor promoters and further confirmation is required on this issue.[38] By all appearances, therefore, fibroblasts from normal skin of polyposis patients behave as if they were "initiated" and are highly susceptible to malignant transformation. This is a promising avenue for the identification of presymptomatic carriers of the polyposis genes, though these techniques are still under development and are not yet widely available for diagnostic purposes.

Chromosomal Aberrations

A number of abnormalities in the chromosomes of lymphocytes or fibroblasts have been observed in patients with Gardner's syndrome and familial polyposis coli, suggesting generalized nuclear instability in these syndromes. The most consistent defect has been seen in chromosome 2, but a variety of random losses and gains of single chromosomes have been reported by Gardner and co-workers.[39]

Increased Tetraploidy in Cultured Skin Cells

Perhaps germane to the above discussions, Danes[40] has reported chromosomal abnormalities in cultures of skin biopsy specimens that possess both fibroblasts and dermal epithelial cells from patients with certain of the inherited colon cancer syndromes. After growth for 6 to 12 weeks in monolayer culture, cells were prepared for examination of mitotic figures. A higher percentage of tetraploid mitosis was seen in the cultures from patients with polyposis than from the controls. The results have been expressed as the percentage of metaphase cells exhibiting in vitro tetraploidy (Table 7). A group of controls (from whom no history of colonic cancer was obtained) was studied, and in 93% of them 0% to 7% of the mitosis was tetraploid, establishing a "normal" range. Only 3% of the controls had more than 9% tetraploidy. Among patients with Gardner's syndrome, 99% had increased in vitro tetraploidy. Among family members who were "at risk" from the families with Gardner's syndrome, 20% showed increased tetraploidy. Curiously, only 15% of patients with familial polyposis coli showed increased tetraploidy, and only 15% of the familial polyposis coli family members "at risk" had this abnormality. Of note, a total of six progeny were studied from the patients with familial polyposis coli, who themselves showed over 7% tetraploidy, and half were abnormal, in contrast with none of the offspring of index patients with familial polyposis coli who had less than 7% tetraploidy. Therefore, this technique appears to identify in vitro an inherited abnormality in most patients who have Gardner's syndrome, in a few of the patients with familial polyposis coli and in a subset of offspring who are "at risk" but in whom polyposis or cancer has not yet developed.

TABLE 7.—*Mechanisms Postulated for Familial Colonic Cancer and Cancer Family Syndrome*

Defective recognitive immunity; impaired response in mixed leukocyte culture[41]
Excessive suppressor macrophages
Various chromosomal aberrations[42,43]
Impaired immune response[42]

Perhaps the most promising aspect of Danes' work is the preliminary finding in patients with familial colonic carcinoma syndromes without polyposis.[40] Of five patients studied thus far, all show excess tetraploidy, and 42% of the family members at risk showed the same abnormality. This unexpected finding identifies a biologic link between the colonic cancer syndromes with and without polyposis, and is possibly a marker for premorbid disease in the latter group. However, these techniques have not been attempted in other laboratories and require additional investigation and confirmation.

Immunologic Abnormalities in the Familial Nonpolypotic Colonic Cancer Syndromes

Much of the investigation into the mechanisms underlying the familial colonic cancer syndromes in the absence of polyposis has focused on dysfunction of the immune system. Berlinger and colleagues[41] have reported a decrease in the responsiveness of lymphocytes to allogenic stimuli in mixed leukocyte culture in three of five such persons. Unfortunately, the other two did not have this abnormality. Also, one of the three who had the defect also had metastatic cancer, and hyporesponsiveness to this type of allogenic stimulation had previously been observed by these authors in persons who had established malignant lesions. It is of great interest that when a group of the healthy first-degree relatives of these patients at risk for the familial cancer syndrome was tested, 8/18 (42%) were found to have the same defect in mixed leukocyte culture. None of 13 persons with familial polyposis coli showed this lack

of immune responsiveness, whereas both patients with Gardner's syndrome were hyporesponsive, again linking Gardner's syndrome pathophysiologically with the nonpolypotic colonic cancer syndromes, as did Danes' work.

Law and associates[42] have reported impaired blastogenic responses to in vitro mitogens in patients with the familial nonpolypotic cancer syndromes and in a proportion of their healthy progeny. Other defects such as impaired skin reactivity to an allogenic tumor antigen and a relative decrease in E-rosette-forming cells were reported in these patients. From a clinical perspective, the scope of the immune deficit must be very selective because affected members in these families do not have other manifestations of immunodeficiency such as unusual infectious complications, and when the tumors are detected and resected at an early stage, long-term survivals are not uncommon. Thus, the significance of these in vitro observations should not be overinterpreted.

Chromosomal Aberrations in the Familial Nonpolypotic Colonic Cancer Syndromes

One final line of investigation has suggested the presence of a variety of chromosome abnormalities in the familial nonpolypotic colonic cancer syndromes. Law and co-workers[42] have reported the occasional occurrence of ring and dicentric forms as well as breaks and fragmentation of chromosomes in affected and nonaffected at risk family members. A very promising development in this area has been the identification of a possible animal model of familial colonic cancer in a South American primate,[43] in which a high rate of spontaneous colonic cancer occurs. Cytogenetic analysis of cultured lymphocytes has indicated an increased susceptibility to mitomycin C-induced chromosomal damage in these animals. If this model should prove appropriate, it could greatly enhance our understanding of the genetically determined susceptibility to cancer of the colon.

Summary

A clinical overview of the familial colonic cancer syndromes has been presented. Those syndromes that are characterized by antecedent colonic polyposis are well known to most clinicians. It has become clear that familial polyposis coli, Gardner's syndrome and the variants of both overlap extensively and represent the multiple clinical faces of a single disease. Research into the underlying mechanism of disease has found abnormalities in the growth characteristics of colonic epithelium in vivo and of cultured skin fibroblasts in vitro. These lines of investigation appear to be leading to a means of making the diagnosis before the first adenoma develops.

The familial colonic cancer syndromes in the absence of polyposis (site-specific colon cancer and the cancer family syndrome) are less well known to most clinicians and may be very difficult to recognize because of the absence of reliable markers of this disease. Research into these syndromes has thus far focused on defects in the immune system and chromosomal abnormalities (Table 7). Preliminary work on cultured skin tissues from a small number of patients has indicated the presence of the same in vitro aberration seen in patients with Gardner's syndrome, suggesting common ground between the polypotic and nonpolypotic syndromes.

The challenge with all of these patients is simple. If one can identify these syndromes before the development of metastatic cancer, patients and their families will be well served. One must only think of the possibility of familial cancer, find the disease early in its natural history and enlighten the appropriate family members of their risks. These syndromes are a challenge to clinicians, and offer investigators an opportunity for further insight into the nature of human cancer.

QUESTIONS AND ANSWERS

DR THOMAS BOYER: *Will in vitro testing of skin fibroblasts be adequate to help counsel patients at risk for familial colonic cancer who are going to be married?*

DR BOLAND: The abnormality in skin fibroblasts has occurred only in patients who have polyposis, who are somewhat easier to identify in the premalignant state because polyps often develop by the time they are in their 20s or 30s. But in a substantial number of those who carry the gene polyps will not develop until later on, and Kopelovich is still cautious in stating that he can definitely detect those asymptomatic persons who carry the gene. He and Gardner have recently published findings suggesting that the cloning efficiency of skin fibroblasts and their response to tumor promoter are promising modalities for screening progeny who are at risk to carry the gene.[44] These tests are not yet widely available, however, and remain primarily research tools. The current projection is that a battery of in vitro tests will be the most sensitive way to identify gene carriers. Ideally, a few centers would be established to support and evaluate these tests.

DR SMITH: *How young have patients been who have been tested in this manner? Is this predictive even in children?*

DR BOLAND: Teenagers and children as young as age 5 have been tested, and the characteristic has appeared even at this young age. However, it will require time to determine how accurate the test is, since most of the young persons at risk who have been tested have not been followed long enough to determine if they actually have the disease. This characteristic therefore appears at a very early age and may be congenital.

DR ROBERT OCKNER: *Were the maturational abnormalities of colonic epithelium also seen in the younger patients?*

DR BOLAND: As with the abnormalities in skin fibroblasts, these changes have also been seen in younger persons (teenagers), antedating the development of

polyposis. It is not known whether this lesion is present from birth. The problem again arises that the progeny tested for this characteristic must be followed long enough to establish presence or absence of the gene before the predictive value of the finding may be evaluated.

DR RICHARD WEISIGER: *A number of oncogenic viruses have been found to contain a single "cancer gene," a form of which is also present in normal genomes. Is there any evidence that an abnormal regulation or dosage of such a gene may be involved in any of these familial syndromes?*

DR BOLAND: This avenue of investigation is only beginning to receive attention. The only study I am aware of has used a single oncogene probe and did not find any evidence to link an abnormality in the expression of that oncogene to familial colon cancer. However, this very fertile topic has yet to be explored in any depth.

DR SMITH: *We have in our audience an expert in the oncogene field, Dr Harold Varmus, who along with Dr Michael Bishop, recently won the Lasker Award for his work with oncogenic viruses. Would you like to comment on this, Dr Varmus?*

DR VARMUS:* I have one comment about recent efforts to identify the gene involved in Gardner's syndrome, and the chromosome on which that gene resides. DNA that is obtained from cultured colonic carcinoma cells may be applied to normal 3T3 mouse cells, and the recipient cells sometimes undergo malignant transformation. The gene responsible for that transformation has been identified as the progenitor cellular homologue of a viral transforming gene called the "ras" gene. Dr Raymond White of Salt Lake City, who has access to some of the large Gardner's syndrome families, has shown by analysis of genetic polymorphisms that the mutation in Gardner's syndrome is not closely linked to the gene identified by the DNA transformation studies. So, it is not the *ras* gene that is involved in Gardner's syndrome.

*Harold E. Varmus, PhD, Professor of Microbiology, University of California, San Francisco.

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Epitomes
Important Advances in Clinical Medicine

Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St, San Francisco, CA 94103

Short-term Chemotherapy for Tuberculosis

THE INTRODUCTION of rifampin and its combination with isoniazid as initial therapy has made it possible to successfully treat tuberculosis in its various manifestations for less than 18 to 24 months. Administering isoniazid, 300 mg, and rifampin, 600 mg, once a day by mouth converts 90% of sputum-positive patients to a negative status within three months. Almost all others will have negative sputum cultures by the end of six months. By giving isoniazid and rifampin for a minimum of nine months, with the proviso that the final six months of treatment be accompanied by negative sputum cultures for *Mycobacterium tuberculosis,* almost all newly diagnosed patients will complete treatment between 9 and 12 months. Monthly visits with sputum examinations for acid-fast bacilli help determine the precise duration of therapy. Adverse drug reactions to isoniazid and rifampin are minimal. These can be recognized by clinical assessment and liver function tests done monthly.

Primary drug resistance has been recognized among initial sputum isolates from immigrants from Latin-American (12%) and Asian-Pacific (15%) countries. For this reason, it is prudent to begin therapy in Hispanic and Asian patients by giving not only isoniazid and rifampin but also a third antituberculous drug, namely ethambutol hydrochloride, 15 to 25 mg per kg of body weight, or pyrazinamide, 1.5 grams, once a day by mouth. These drugs should be taken until drug susceptibility tests are reported. For those patients with organisms susceptible to isoniazid and rifampin, the third antituberculous drug can be discontinued; for the rest, triple drug therapy should be continued throughout the treatment period. Isoniazid should not be discontinued despite in vitro resistance as it has a therapeutic effect on tubercle bacilli in vivo.

Relapses or recurrence of positive cultures for *M tuberculosis* occurring after the completion of appropriate chemotherapy are infrequent following short-term chemotherapy. Almost all relapses occur during the six months after completion of therapy. The organisms that reappear under these circumstances have the same drug susceptibility patterns that were present before initial chemotherapy. Reinstitution of antituberculous chemotherapy for at least a year is usually successful.

Short-term chemotherapy is also applicable to those patients who, for a variety of reasons, do not or cannot take their daily medicine on a voluntary basis. By identifying those patients through an initial compliance assessment—that is, behavioral, cultural, psychologic and other life-style factors that are frequently associated with noncompliance—a treatment program consisting of intermittent supervised chemotherapy can be designed that will ensure a successful outcome. Isoniazid, 15 mg per kg, and rifampin, 600 mg, are administered twice a week by mouth by a responsible person (family member, clinic personnel, community worker or the like). Where there is concern regarding initial resistance to isoniazid, either ethambutol (50 mg per kg) or pyrazinamide (2 to 3 grams) is given in addition to the isoniazid and rifampin. A treatment period of 9 to 12 months will suffice provided that the sputum cul-

tures for acid-fast bacilli are consistently negative for the final 6 months. Despite the high incidence of patients with preexisting liver disease within the noncooperative group, adverse liver reactions due to isoniazid, rifampin, and pyrazinamide are remarkably infrequent.

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Exposure of Expectant Mothers to Cytomegalovirus Infections

HUMAN CYTOMEGALOVIRUS (CMV) infections are common worldwide. The epidemiology of this virus has not been completely delineated but it is known that transmission from person to person requires intimate contact. Among adults, the primary route of transmission is by intimate (oral or sexual) contact. Most cytomegalovirus infections are asymptomatic or mild.

Infection with cytomegalovirus has particular significance for pregnant women. The virus can infect the fetus in utero following a primary infection in the mother and, unlike rubella, also by reactivation of latent maternal cytomegalovirus. The risk of manifest congenital disease at birth appears to be largely associated with a mother's first (or primary) infection during pregnancy but the relative contribution to fetal damage by reactivated maternal cytomegalovirus infections has yet to be defined. In the United States 0.5% to 2.2% of all newborns are congenitally infected as shown by viral excretion at birth but most of these infected infants show no clinical signs of impairment at delivery. About 10% of these infections (about 1 per 1,000 births) result in some overt congenital cytomegalovirus disease at birth, but some of the asymptomatic congenital infections may produce effects detectable only later in life.

The results of several studies suggest that from 3% to 28% of all pregnant women in the US shed cytomegalovirus from their cervix by the third trimester of pregnancy. The virus has also been detected in the breast milk of 13% of women with cytomegalovirus antibodies. Such viral shedding is thought to be due predominantly to the reactivation of latent infection during pregnancy. Infants born to mothers shedding this virus may be infected connatally—that is, during labor or at birth—or postnatally. Most connatal and postnatal infections, like those acquired in utero, are asymptomatic, but some of these infections may conceivably produce subtle effects, the long-term results of which have not been well documented. Studies in the US also indicate that up to 30% of all children acquire cytomegalovirus infections by 3 years of age. Avoiding or reducing the risk of exposure to cytomegalovirus is difficult because of the large number of asymptomatic virus shedders in the general population.

Whether women who provide care to any group of infants and children have a greater risk of acquiring a primary infection with this virus than women not so employed has not been established. The most important routes of cytomegalovirus transmission from children to adults are apparently via contact with urine or saliva of virus shedders, for example, through kissing or poor personal hygiene after handling soiled diapers. Thus, nursery and other child care staff who are in contact with known infected infants and who adhere to routine patient care practices such as handwashing should not be at increased risk of acquiring a cytomegalovirus infection.

Women of childbearing age should be informed that this virus is ubiquitous and that prevention of infection from infants and children in any setting (home or occupation) is best accomplished by observing good personal hygiene. These women should also be advised that this virus is of relatively low infectivity, and, in contrast to the transmission of rubella and rubeola infection, intimate contact is usually required to transmit it. Antibody testing programs for women who are routinely in close contact with children cannot be recommended at the present time, since there is no information to indicate (or suggest) that such a program would reduce the risk of congenital damage to infants infected with cytomegalovirus.

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Exposure of women to cytomegalovirus infections in medical and educational facilities. California Morbidity Supplement No. 7. Berkeley, Calif, State Department of Health Services, Feb 25, 1983

Stagno S: Isolation precautions for patients with cytomegalovirus infection: An interview with Sergio Stagno. Pediatr Infect Dis 1982 May/Jun; 1:145-147

Office Treatment of Alcoholism

MOST PHYSICIANS have been trained in public hospitals to recognize alcoholism by a patient's end-stage liver disease or other serious sequelae of heavy drinking. Patients who are obviously alcoholic represent only 5% or so of those who will go on to die an average of ten years prematurely because of their alcohol-related problems.

The average alcoholic person is a blue-collar or white-collar worker or a homemaker who drinks too heavily on evenings or weekends or experiences short periods each year when alcohol problems escalate. In these persons, who compose 15% to 20% of the patients seen in practice, cirrhosis rarely develops (seen in only 15% of alcoholic persons), and they are unlikely to enter a physician's office in an intoxicated state. The fall of blood alcohol concentrations to zero on an almost daily basis results in a moderate to mild withdrawal syndrome that, for 95% of these persons, causes tremor, anxiety and a flulike feeling.

Recognition of this average middle-class alcoholic person is important to clinicians because such patients are not likely to respond in a predictable way to therapeutic intervention if they continue drinking. Patients usually have nonspecific complaints, perhaps request a physical examination, and are likely to have mild hy-

pertension (about 140/90), mild elevations in any one or more of a number of laboratory values (uric acid, γ-glutamyl transferase, triglycerides, mean corpuscular volume) or have symptoms of insomnia, impotence or depression. The diagnosis is made by asking a patient (and spouse, if appropriate) about the pattern of life problems and then determining whether alcohol was a contributor. These problem areas include family (a separation or divorce related to alcohol), police (two or more alcohol-related arrests or accidents), job (an alcohol-related loss or layoff) and health (physical evidence that alcohol intake had harmed health, including a history of alcohol withdrawal). Once alcoholism has been identified, confrontation entails reminding patients that they are responsible for their own actions, pointing out ways in which alcohol use has significantly interfered with their life, noting that a long and healthy life will require abstinence and referring them to a treatment program or Alcoholics Anonymous (or both).

The prognosis in alcoholism is good. The chances that a patient will achieve and maintain abstinence for an extended time (longer than a year) increase with the patient's level of stability before entering care. Thus, a person who has an intact family, a job or relevant job skills and an absence of drug problems or non-alcohol-related police difficulties has a 70% chance of being abstinent for one to two years.

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Car Passenger Injuries and Child Restraints

THE USE OF appropriate restraining devices (car seats and safety belts) for child car passengers is truly an idea whose time has come. Few health service agencies, such as hospitals, clinics, medical or dental offices, pharmacies or health departments, actively promoted these devices until a short while ago. For children under 15 years, car passenger injuries represent the single leading cause of death in the United States, almost 2,000 fatalities per year.

The younger a child, the more vulnerable he or she is to severe injury or death. Considering the anatomic proportions of children, this finding is not surprising: a relatively higher center of gravity makes a child, when unrestrained, serve as a projectile hurled inside or outside a car when it is stopped by a crash or sudden braking. The "typical" child victim is a 1-year-old who rode unrestrained in the front seat of the family car, and the injury occurred during the daylight hours and in ordinary weather and road conditions.

There is no question that child restraints provide significant protection; unrestrained children are more than ten times as likely to sustain severe injury or death. Tennessee, the first state to enact mandatory child restraint legislation in 1978, reports a provisional 50% reduction in fatalities. About 30 other states have recently enacted similar legislation mandating car seat or safety belt use by young children.

Through education of their parents, children should be protected against car passenger injuries. Ideally this activity should be initiated during the prenatal period and proceed on through infant restraints to include the use of safety belts by school-age children. This simple, sensible and safe practice will not be easy to implement universally but can be accomplished through a combination of health education, legislation and the development of an increased personal sense of health and safety.

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Screening for Colorectal Cancer

COLORECTAL CANCER is the second most common type of cancer (excluding skin cancer) in the United States. In 1983 there will be an estimated 126,000 new cases (87,000 colon and 39,000 rectal) with about 58,000 deaths.

The American Cancer Society has issued the following guidelines for colorectal cancer checkups:

- Men and women over 50 years of age should have a test for occult blood in the stool every year;
- men and women over 50 years of age should have annual sigmoidoscopic examinations until two consecutive examinations are normal and thereafter every three to five years, and
- men and women over 40 years of age should have a digital rectal examination yearly.

Persons who are at a high risk of colorectal cancer developing should receive more frequent and intensive examinations beginning at an earlier age. High-risk groups include persons with a history of adenomatous colon polyps or prior colon cancer, Gardner's syndrome, ulcerative colitis, familial polyposis or a family history of colorectal cancer.

The National Cancer Institute's consensus report states that the stool blood test should not be used as yet for screening, until the outcome of ongoing clinical trials shows a decrease in colorectal cancer mortality. The Canadian Cancer Society recommends that the screening use of stool blood test be used only for persons at high risk.

One must realize that most but not all colorectal cancer patients will have occult blood in the stool and that some but not all precancerous colorectal lesions (for example, adenomatous polyps) will bleed; other non-neoplastic conditions may give a positive test for

blood. One must also accept the cost and risk of the workup when occult blood is found in stool specimens, to be able to detect colorectal cancer at an earlier stage and improve the prognosis. I favor the American Cancer Society's recommendations for the present instead of awaiting the results of clinical trials.

The International Workgroup on Colon Rectal Cancer has recommended that fecal occult blood testing be done annually beginning between the ages of 40 and 50 years.

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Prevention of Hepatitis B Virus Infections From Mothers to Infants

WHILE RELATIVELY UNCOMMON in the United States, chronic infection with hepatitis B virus (HBV) may be found in up to 15% of the population in many developing countries. A significant proportion of these infections occurs as a result of mother-to-infant transmission. Persons chronically infected with HBV, especially those infected at birth or early in life, are at increased risk of subsequent liver disease such as chronically active hepatitis, cirrhosis and primary hepatocellular carcinoma.

In California alone (an area of low incidence), an estimated 3,000 to 5,000 women who are positive for hepatitis B surface antigen (HBsAg) give birth each year. Most mother-to-infant infections seem to occur at the time of delivery (connatal) or shortly thereafter, rather than transplacentally. The probability of exposed neonates becoming HBV carriers can be greatly reduced by administering hepatitis B immune globulin. The Public Health Service Immunization Practices Advisory Committee (ACIP) recommended in 1981 that all infants born to HBsAg-positive mothers should be given 0.5 ml of hepatitis B immune globulin immediately after birth and at three and six months. The Committee on Infectious Diseases of the American Academy of Pediatrics has made a similar recommendation.

In June 1982 the ACIP recommended that infants born to HBV-infected mothers should also receive hepatitis B virus vaccine, in addition to the three doses of hepatitis B immune globulin, inasmuch as these infants may continue to be at risk of infection from their mothers and other possible carriers in the household. The optimal timing for giving the vaccine in conjunction with hepatitis B immune globulin has not yet been established. Until additional data are available, however, the ACIP has recommended that immunization with hepatitis B virus vaccine should be started at three months of age, or shortly thereafter.

To carry out appropriate prophylactic measures in the delivery room, it is necessary to know before delivery whether the mother has the hepatitis B surface antigen. The HBsAg carrier rate in the US population ranges from 0.1% to 0.5%. Much higher HBsAg carrier rates are found in persons from hyperendemic hepatitis B virus areas of the world, such as Asia, Subsaharan Africa and the Pacific Islands. Persons of Asian ancestry born in the United States appear to maintain relatively high HBsAg carrier rates. There are thus clear indications for doing routine prenatal HBsAg testing of women who are members of groups with HBsAg carrier rates of 1% or more. In addition to the ethnic minorities already mentioned, these groups include women who have acute or chronic liver disease, frequent occupational exposure to blood, household or sexual contacts of known HBsAg carriers and women with a history of injecting illicit drugs.

The prevention or modification of hepatitis B virus infections in infants deserves high priority as there is no present cure or treatment for the chronic HBsAg carrier state once it is established. Additionally, failure to identify pregnant carriers in the known high-risk groups can expose health care providers to an increased risk of nosocomial hepatitis B and to possible legal action on behalf of those infants in whom the chronic carrier state might develop because of the failure to provide any prophylaxis.

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Pesticides as a Public Health Concern in California

CALIFORNIA LEADS the nation both in the volume of pesticides used and in the number of pesticide-related illnesses. In 1981 the statewide use was 218 million kg (480 million lbs) of pesticides, 78% of which was for agriculture, the remainder for home, garden, structural and industrial use. Last year, 1,388 illnesses related to occupational exposure to pesticides were documented in the state, 48% of which involved systemic symptoms, the rest being skin and eye conditions. This information is based on physicians' reports of pesticide illness and investigations by agricultural and public health agencies. The State Health and Safety Code requires that any physician "who knows, or has reasonable cause to believe, that a patient is suffering from pesticide-related illness" must report the case to the local health officer within 24 hours; also, in work-related illness, a "Physician's First Report" of illness must be filed within seven days. Failure to comply with the reporting requirement renders the physician liable for a civil penalty of $250.

The high-risk occupations for systemic pesticide illness are mixing, loading and applying of pesticides,

particularly fumigants and organophosphates. Also, workers harvesting fruit and vegetable crops accounted for 362 illnesses. The problem of field worker poisoning is most pronounced in coastal areas where highly toxic organophosphates (for example, mevinphos) and carbamates (for example, aldicarb) are applied to row crops shortly before harvest. The State Agriculture Code for specific pesticides requires that workers not reenter treated fields until pesticide residues have degraded to levels that should not result in acute worker illness. However, dermatitis, the most common field worker illness, and systemic poisonings from dermal absorption of organophosphates do occur because workers are sent into fields before the reentry interval expires.

Clinicians who wish a handbook review of the subject may request the manual *Recognition and Management of Pesticide Poisonings* from the Environmental Protection Agency. The definitive text on the subject is Wayland Hayes' recently published *Pesticides Studied in Man.*

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International Travel Requirements

TRAVELERS WHO SEE physicians before traveling abroad usually do so because of the perceived need for a required immunization. More often than not these immunizations are not required, but other immunizations, chemoprophylaxis and advice are much more important for a traveler's health.

Only two immunizations can be legally required of civilian travelers. (Smallpox has been officially eradicated with the last reported endemic case in 1977, and no country presently requires smallpox immunization.) Countries requiring immunization against cholera or yellow fever (or both) can refuse the right of entry to travelers who have neither a valid immunization recorded on the International Certificate of Vaccination nor a written statement from a physician indicating why immunization was contraindicated. An annually updated list of required immunizations by country is provided by the Public Health Service in the Information for International Travel Monograph, available from the Centers for Disease Control, 1600 Clifton Rd, NE, Atlanta, GA 30333.

The risk of cholera in travelers with normal gastric acid is minimal. Nevertheless, many countries require cholera vaccine for all travelers or for those coming from a cholera endemic area, therefore, cholera immunization is often given to travelers to prevent border hassles. One injection of the presently available killed cholera vaccines will meet international requirements, and, after a six-day waiting period, is valid for six months. Cholera immunization is not recommended or required for infants.

Yellow fever, limited to tropical Africa and South America, can be prevented by a single injection of attenuated 17D live virus vaccine; the certificate of vaccination is good for ten years after a ten-day waiting period. Yellow fever vaccine is not recommended for infants less than 1 year of age, for pregnant women or for immunocompromised persons. Correct handling of the vaccine, described in detail on the label, is essential.

In addition to immunizations that may be required, all children should have their childhood immunizations up to date. Adults should be urged to have a tetanus booster and live oral poliovirus vaccine if they have not been immunized with these agents within the past ten years. Adults who have not previously received oral poliovirus vaccine or whose polio immunization record is uncertain should receive parenteral (killed) poliovirus vaccine to avoid the small risk (1 per 11 million doses) of paralytic poliomyelitis associated with live oral poliovirus vaccine. Travelers to developing countries may also be given typhoid vaccine: three doses are recommended but a single dose, all that many travelers have time for, offers some protection. γ-Globulin is recommended to reduce the risk of hepatitis A. When necessary, all active immunizations can be given at separate sites on the same day. γ-Globulin, however, may interfere with antibody response to active immunization and should be given at least two weeks, and preferably four, after the vaccines. Because γ-globulin protection wanes over time, it should be given only a few days before departure.

Other vaccines occasionally recommended for travelers according to itinerary and life-style are plague, rabies and bacille Calmette-Guérin (BCG) against tuberculosis; few persons who travel for pleasure need these vaccines. Typhus vaccine is not recommended for travelers, nor is it available in the United States.

Few travelers come to a physician seeking antimalarial drugs. Physicians must match the itinerary against the malaria transmission by country data provided in the Information for International Travel Monograph. For most travelers to most malarious areas a weekly (300 mg base) dose of chloroquine throughout the entire period of exposure and for six weeks thereafter will suffice. This should be started one to two weeks before exposure to be sure that the medication is tolerated. Except for a few persons who are chloroquine intolerant (vomiting and malaise being the most common side effects), chloroquine can be given safely to all travelers, including children and pregnant women. Chloroquine-resistant falciparum malaria is seen in Southeast Asia and some parts of South America and East Africa. Travelers to these areas, as detailed in the monograph, should receive Fansidar (Hoffmann-La Roche) in addition to chloroquine. Fansidar is a newer antimalarial agent, each tablet contain-

ing 500 mg of sulfadoxine and 25 mg of pyrimethamine. One tablet of Fansidar is taken weekly at the same time and for the same duration as chloroquine. Fansidar is not recommended for young children or pregnant women. ELIZABETH BARRETT-CONNOR, MD

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Toward the Elimination of Measles

BEFORE INTRODUCTION of the measles vaccine in 1963, 500,000 cases of measles (rubeola) were reported yearly in the United States, though the actual case number was much higher. Also, 500 deaths and 1,000 cases of neurologic damage occurred yearly. In the first few years after the vaccine came into use measles incidence dropped 90%, but it declined no further through most of the 1970s. The reasons were that only 60% of US children were being immunized and that vaccine failure was common, due to the use of an ineffective inactivated vaccine in the early years, failure by some to adequately protect the live vaccine from heat and light and administration of live vaccine at too early an age. (In children under age 13 months, persisting maternal antibody may interfere with immunization.)

Measles has no nonhuman reservoir and no carrier state, and the measles vaccine confers long-term, probably lifelong, immunity. Consequently, in 1978 the Centers for Disease Control launched a campaign to eliminate continuing indigenous measles transmissions from the US by late 1982, based on a strategy of near-universal immunization and intense disease surveillance and outbreak control. We have come remarkably close to this goal. In 1982 only 1,700 cases were reported nationwide, a 99.7% drop from prevaccine era incidence. In all, 94% of US counties remained entirely measles-free in 1982. The principal reason for this achievement was enactment and strengthening of laws requiring measles immunization for entry to schools and child care centers in all 50 states during the late 1970s. Current surveys indicate that each year 96% of the nation's kindergarten pupils have satisfactory evidence of measles immunization.

Sporadic measles outbreaks still occur, however, particularly in large urban populations repeatedly exposed to measles importations and with lower immunization levels in older school pupils, who entered school before the immunization laws were strengthened. Several states are currently acting to improve the protection of older pupils, requiring that they provide schools with records showing at least the month and year of immunization with live measles vaccine given no earlier than the first birthday. In addition to giving measles vaccine to children at age 15 months and to all patients age 25 years and under who have not already been immunized or had the disease, physicians are urged to reimmunize those who received vaccine before their first birthday, when the seroconversion rate may have been only 80% to 85% or even lower, compared with 95% for immunization at older ages. Some authorities also recommend reimmunizing certain children previously immunized between 12 and 13 months of age.

Another major reason for the recent decline in measles incidence has been the public health effort to locate foci of continuing measles transmission and to eradicate these foci by prompt ring immunization. Physicians are urged to report immediately to county health departments by telephone all cases of measles, suspected measles and generalized rash with fever, without waiting until a definite diagnosis is made. Health departments can then promptly investigate and, if a focus of measles is found, define a zone of risk around the case(s) and immunize and isolate susceptible persons within that zone. LORING DALES, MD

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Editorials

Some Realities in Cost Containment

It is generally recognized that this nation has the best health care system in the world and also that it is the most expensive. Understandably, those who pay the bills are the most concerned about the costs, and those who receive the benefits, less so—whether they be patients or providers of care. Government and more recently business and labor, have begun to give high priority to the containment of costs in health care, and this is not likely to change in the foreseeable future. So far the efforts to contain these costs through regulation and in other ways have frequently been relatively ineffectual, have only scratched the surface of the problem, and have too often been shown by experience to have increased rather than reduced costs. It seems time that some realities be taken more into account in the approaches to cost containment.

Three Seminal Realities

Three realities seem to be of seminal importance. First, science and technology will continue to advance and this will inevitably generate higher costs. What has happened in the last few years in the care of myocardial infarction and coronary heart disease attests to this. And science and technology are probably only at the threshold of what can and will be done not only for this but for many other conditions as well.

Second, the people of this nation place a high value on human life, a high value on health and on access to health care. For instance, we cannot even seem to bring ourselves to execute convicted criminals who have been fairly tried and sentenced to die because of their heinous and often hideous crimes against their fellow man. Another illustration is the strong sentiment in high places for preserving the lives of hopelessly deformed or impaired newborn infants without regard to the quality of life they may expect or the emotional or fiscal cost to others that might result. Also, the many programs to bring better health care to medically underserved areas and populations are examples. The social value we place on life, health and access to care is surely a seminal force that clearly drives the cost of health care higher, and this is not likely to be reversed very soon.

Third, there must eventually be some limit to the amount of public, personal or community resources that people are willing to devote to health and health care. It has just recently been reported that the national expenditures for health have exceeded 10% of the gross national product for the first time. It is obvious that at some point and in some way there will need to be some cap or ceiling on expenditures for health.

Some Artificial Inflatants of Health Care Costs

There is another set of realities that has produced artificial inflation in health care costs. Some of these are at least potentially reversible, but to reverse them will require some basic changes.

1. The earliest health insurance programs provided better coverage for hospital care and for surgical and other procedures in patient care. This emphasis has continued to the present and the fiscal incentives persist for both provider and patient to make use of the benefits for which the coverage is good. Efforts are being made to provide better coverage for less expensive and often cost-saving modalities of treatment such as cognitive services and out-of-hospital care, but progress has been slow.

2. It is by no means certain that many generally accepted methods of treatment are truly effective. The long accepted but now largely discredited Halsted operation for cancer of the breast is a case in point. It seems more than likely that many health care dollars are being spent for care that is believed to be effective but actually may not be.

3. Failure to realize economies of scale also artificially inflates the cost of health care. When procedures, surgical or otherwise, are done frequently in a centralized location, the true costs are usually less and the quality often greater. The reality is that the charges are seldom lowered as experience and efficiency improve.

4. Defensive medicine adds enormously to the cost of health care. This is an artificial added cost that has very little to do with patient care other than to make it more costly for patients and for the public. The costs of this are substantial. One can only speculate on the extent to which some kind of no-fault insurance would lower the cost of health care.

5. Increasing administrative paper work and bureaucratic hassles have come to add substantially to the cost of care wherever it is rendered. This added cost is necessary for compliance with the myriads of laws and regulations that have been imposed upon the health care system in efforts to regulate it and to control the dollars spent. Some of this added administration and its attendant costs is needed and useful, but certainly not all.

One can only guess at what the total impact of realities such as those just mentioned above might be on the cost of health care. Many costs could be substantially reduced if we as a nation were to change some of our ways of doing things. Clearly these are examples of realities that won't go away unless someone does something about them. The medical profes-

sion can help by calling attention to artificial inflatants of the cost of care such as these, and can begin to document the extent of their impact.

A Final Reality

A final reality is that no matter how much "fat" is trimmed from health care costs by reducing the artificial inflators or by any other means, the three seminal realities stated at the outset will ultimately prevail. Somewhere, somehow people will have to decide what they are willing to have available and what they are willing to pay for in health care. It seems to this writer that the more locally these decisions can be made the better. There is considerable experience to suggest that a centralized federal or even a statewide approach (in the larger states at least) is unlikely to work. Some sort of local or regional confederation or alliance may be needed where people in the public and private sectors can make the hard decisions together in terms of local needs, local customs, and the local and regional resources that the people themselves are willing to allocate to their health care. This is not exactly the pro-competition approach now being espoused, but it would surely stimulate competition and also cost containment in health care.

MSMW

Advances in Oncology

Elsewhere in this issue, Morton and his colleagues have focused on three areas of current therapeutic research interest in clinical oncology. These include the use of doxorubicin hydrochloride (Adriamycin)-based adjuvant chemotherapy for extremity sarcoma, regional hyperthermia as a new treatment modality and the in vitro human tumor stem cell or clonogenic assay for assessing effects of anticancer drugs as a "culture and sensitivity" test. These topics are not uniquely "surgical"; in various centers, they are being pursued by oncologists with a variety of disciplinary (or, more appropriately, interdisciplinary) interests.

Therapy for extremity sarcoma has been difficult, and the use of only surgical intervention in the past had largely mandated an aggressive approach, with amputation a virtual certainty. The innovative approach taken by the University of California, Los Angeles (UCLA), group, using a combination of preoperative intraarterial chemotherapy followed by radiotherapy, limb salvage surgical procedure and postoperative adjuvant chemotherapy, has had very encouraging results and may well be a major contribution to the management of these uncommon neoplasms. Their results in extremity recovery indicate that this procedure, while not totally uncomplicated, can provide satisfactory local control of extremity sarcoma similar to that which can be achieved with amputation. A recent report by Rosenberg and co-workers at the National Cancer Institute[1] of a prospective randomized trial that addressed the issue of amputation versus saving a limb for patients with locally resectable extremity sarcoma has confirmed the validity of the approach espoused by the UCLA group. In the exploratory studies of the UCLA group, they used a combined modality approach for all patients, and it is difficult to dissect the relative contribution of each component. While the results of Rosenberg's study appear comparable, they did not use preoperative chemoradiotherapy, but rather relied on postoperative adjuvant chemotherapy.[1] They clearly established that the addition of chemotherapy improved disease-free survival in patients with soft tissue sarcoma of the extremities in whom surgical resection of the primary lesion was done. It seems reasonable to suspect that more patients may have been rendered locally resectable with preoperative therapy, as used at UCLA. This approach would appear to warrant more widespread application, as it could significantly reduce the need for amputation in patients with extremity sarcoma. This approach should become even more applicable if more effective drugs are identified that synergize with doxorubicin.

The application of regional or local hyperthermia as a treatment for cancer may be age-old, but the scientific foundations for this approach have been developed more recently. Major clinical research applications of hyperthermia appear to be primarily directed towards therapy for large tumors, which show enhanced susceptibility to hyperthermia, particularly in concert with radiotherapy.[2] A variety of regional heating methods, including propagated wave and inductive techniques, are now being studied in many centers.[3] No one technique appears clearly superior for all sites at this time for the various applications of hyperthermia. Rather, ultrasonic and electromagnetic techniques for producing local and regional hyperthermia have specific advantages and disadvantages, such that they may be used more profitably in the near future in a complementary manner.[3] Despite advances in instrumentation, there are still major limitations in the approaches available to heat deep-seated tumors and specific regional sites. Whereas Storm and his colleagues at UCLA have claimed that their approach using magnetic-loop induction hyperthermia provides an effective means of heating visceral organs, this claim is viewed as controversial. Other groups have observed nonuniformity of regional heating, specifically an inability to raise temperatures of deep-seated tumors to therapeutic (42°C or higher) temperatures and in other cases, associated systemic heating, with this technique.[4,5] Part of the problem in assessing hyperthermic fields has been the lack of techniques suitable for noninvasive thermometry. A number of investigators are hopeful that hyperthermia will prove to be a useful adjunct to the management of tumors at specific sites; however, controlled clinical trials are needed to clearly define the efficacy of hyperthermia and to determine its role in cancer management.

With respect to the human tumor stem cell or clonogenic assay, the results obtained and the perspectives espoused by Kern of UCLA are consonant with those recently put forth in several articles.[6,7] Other groups

remain skeptical or nihilistic.[8] When our group first developed and reported chemosensitivity results with this procedure, we cautioned that both further methodologic development and extensive clinical testing would be required with this assay procedure.[9] Some clear progress has been made in this field, and most workers who have carried out either retrospective analyses[10-12] or prospective clinical trials[13,14] have found, in fact, that the assay can predict clinical drug resistance quite accurately and drug sensitivity with reasonable accuracy. Kern has accurately delineated many of the persisting problems with this procedure, including the inadequate in vitro growth rates for some tumors (such as breast cancer and lymphoma) and the varying criteria for sensitivity applied by some laboratories in lieu of adequate correlative data to validate their approach. Limitations in growth rates with this procedure and the lack of effective drugs for many common tumor types (such as colon, renal and non-small cell lung cancer) indicate that the assay cannot yet be considered a routine procedure for most cancerous neoplasms.

While there is no risk to a patient in sending a portion of a primary tumor for cell culture, correlations have yet to be reported between in vitro sensitivity of primary tumors and the efficacy of adjuvant chemotherapy or the subsequent response of metastatic lesions. On the other hand, it is difficult to justify a major operation to obtain tumor specimens for in vitro assay except in a research setting wherein the benefits and risks can be evaluated. Thus, at present most investigators deal primarily with readily accessible metastatic nodules or with malignant effusions present in patients with far advanced cancer. Some selective clinical applications of the assay do appear reasonable, but this procedure must still be viewed as evolutionary.

While large randomized clinical trials may eventually be of some help in evaluating the impact of the clonogenic assay on patient management, such trials will not be feasible for most tumor types until growth rates in vitro improve and effective drugs become available. Our current preference in clinical trial design is the *prospective correlative trial design,*[15] wherein biopsy of a patient's tumor is done, therapy using a specific agent is begun and that drug is definitely tested in the laboratory. The results of the in vitro test can be kept independent of the clinical trials and subsequently compared to assess correlation. The assay appears so far most applicable to advanced ovarian cancer, as tumor tissue can usually be taken readily, growth rates are relatively good in vitro and there is a reasonable spectrum of anticancer drugs that exhibit both in vitro and in vivo activity.

Whereas the goal of an individualized chemotherapy regimen has been a major objective for many researchers using the human tumor clonogenic assay, this may not prove to be its most important application. The ability to clone human tumors in vitro has already greatly increased study on human cancer biology[16-19] and has also provided a new approach to drug development.[20,21] Currently, the National Cancer Institute is evaluating the procedure to determine whether or not it will prove a more useful model with which to identify entirely new drugs in its screening effort.[22] Should this application prove successful, the pace of therapeutic advancement in clinical oncology may quicken perceptibly.

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On Drug Education for Patients

THE RECENT DEVELOPMENT of patient medication instruction (PMI) sheets by the American Medical Association for physicians to give to their patients, and the even more recent (July 1983) distribution of approximately 36 million letters from the Food and Drug Administration (FDA) to the recipients of Social Security checks urging them to ask questions such as the name of the drug they are taking, what its intended uses and side effects are, and what foods or drinks should or should not be taken with the medicine, mark

yet another step in the evolution of what might be called the *nouvelle* health care for patients—and others for that matter. It is becoming clear that both the profession and the public are now coming to view physicians and patients as more or less equal partners in patient care.

This sharing of responsibility with patients should improve results in patient care by improving communication and a patient's understanding of what needs to be done and what may be expected. This is all to the good. It is particularly likely to be true of better educated patients who genuinely wish to understand their health problems and the purpose and use of the medicines prescribed. But these are not all the patients seen by physicians. One cannot help wondering if this principle always holds true if a patient is apprehensive, fearful, not well educated or perhaps even distrustful of the whole health care system because of cultural beliefs or some other reasons. This "nouvelle approach" to health care, particularly when it bypasses the physician in the care of a patient, poses many challenges and also provides many opportunities for conscientious and caring physicians who strive to match the art and science of medicine to the particular needs of each patient.

MSMW

Cardiotoxic Effects of Anthracyclines

ELSEWHERE IN THIS ISSUE, Saltiel and McGuire review the topic of anthracycline cardiotoxicity, a new and totally iatrogenic disease that has generated considerable interest in recent years. The reasons for this interest are several and include (1) the perceived clinical importance of anthracycline cardiotoxicity, a devastating adverse effect of this most useful and promising class of chemotherapeutic agents, (2) the unique quality of cardiotoxic reaction as a side effect of a chemotherapeutic agent and (3) the fascinating complexity of the mechanism(s) of action of the anthracyclines. I will discuss each of these features from my own point of view, and comment on the positions outlined in the review.

As discussed by Saltiel and McGuire, heart failure from dose-related cardiomyopathy is the most clinically important form of anthracycline cardiotoxic effect. This diffuse form of biventricular heart muscle disease is usually a devastating illness that, as first pointed out by Benjamin,[1] is a disease worse than any form of cancer. Almost every practicing oncologist has encountered such a case, and this experience inculcates a healthy respect for anthracycline cardiotoxicity. The imprint of this experience is such that fear of anthracycline cardiotoxicity may lead to underuse of doxorubicin (Adriamycin), the most important single chemotherapeutic agent available to oncologists. Such concern, however, need not limit the use of anthracyclines, any more than fear of marrow suppression limits the use of anticancer drugs. The idea is to learn as much about the problem as possible, and use these drugs in such a way as to minimize the risk of cardiotoxic reaction.

As outlined by Saltiel and McGuire, there are excellent noninvasive and invasive methods for cardiac monitoring during the administration of anthracyclines. Our own recommendations on how to use them[2-4] differ somewhat from those of Saltiel and McGuire in that we do not recommend cardiac monitoring of patients who do not have "risk factors" of previous cardiac radiation, age more than 70 years, previous anthracyclines to a total dose of more than 450 mg per sq m or underlying heart disease including a history of hypertension. In nonrisk patients the extremely low incidence (less than 2%) of heart failure does not justify the cost of cardiac monitoring.[3] For risk-factor patients we recommend either serial radionuclide ejection fractions done at rest and with exercise and with biopsy-catheterization evaluation of abnormal values,[2-4] or biopsy and catheterization only.[3] We[3-5] and others[6] have found that endomyocardial biopsy with morphologic grading according to the Billingham method,[3-6] combined with right heart catheterization, is quite reliable in making dosing recommendations.

The second reason for widespread interest in this subject is the uniqueness of anthracycline cardiotoxicity. Although a few other chemotherapeutic agents have shown "idiosyncratic" cardiotoxicity[7,8] or cardiac toxicity at ultrahigh doses,[9] no other class of agents causes an inexorable dose-related cardiac toxic effect in the manner of the anthracyclines. Sensitivity to the drug varies among individual patients[10] or animals,[11,12] but in each subject a progressive amount of cardiac damages will develop as more drug is given.[10] From a cardiologic standpoint, this process amounts to an extremely useful model of diffuse heart muscle disease, as in a matter of months a cardiomyopathy is created de novo.

Several aspects of this model of diffuse heart muscle disease have practical significance. In patients with cardiotoxic effects of anthracyclines, symptoms of heart failure appear to develop suddenly, and subclinical cardiac dysfunction also develops quite rapidly.[10,13] In uncomplicated cases significant dysfunction occurs when 20% to 25% of heart cells become involved.[10,13] This "nonlinear" form of structure-function relationship means that to be 100% sensitive, noninvasive measurements of cardiac function will have to be done quite often in order to detect the sudden functional deterioration that may result in heart failure. In "Adriamycin equivalents" this interval is every 60 to 120 mg per sq m, or every one to two doses. But because the dose-morphologic damage relationship is linear,[10] when endomyocardial biopsy is the means used to guide therapy this test need not be done as often, as "confidence intervals" of 100 to 200 mg per sq m can be given.[3] Moreover, as noted by Saltiel and McGuire, endomyocardial biopsy is the only method of detecting anthracycline effect at doses below the level at which cardiac function deteriorates. Biopsy is therefore the method of choice for evaluating analogues in phase II trials wherein doses may not be large enough to alter function. Morphologic monitoring, however, must use

glutaraldehyde-fixed specimens and electron microscopy, as routine light microscopy is not adequate for detecting anthracycline effect.[14]

A final point that has led to widespread interest in this topic is the complexity of the mechanism of action of this class of agents. The diverse cellular and subcellular effects of these compounds are such that it is difficult to give a complete review of the subject, and some potentially important actions of anthracycline are not included in the Saltiel and McGuire paper. Anthracycline antibiotics intercalate with DNA and inhibit DNA and RNA synthesis,[15] promote the synthesis of free radicals,[16,17] inhibit the mitochondrial respiratory chain enzyme ubiquinone,[18] alter calcium flux,[19-22] bind to and alter the physical properties of contractile proteins,[23] alter cell surface properties[24,25] including membrane fluidity,[25,26] inhibit guanylate cyclase[27] and are a potent stimulus for the release of vasoactive or cardioactive hormones from heart and other tissues.[12,28,29] This cornucopia of effects insures that the anthracyclines offer something for everybody's favorite tumoricidal or cardiotoxic hypothesis. Because of this pharmacologic complexity, the wisest approach to the study of anthracyclines would probably be to ban them from one's laboratory. For those of us who do not possess such intelligence, it is important to keep certain things in mind:

- Anthracyclines are cytotoxic drugs that affect a wide variety of systems (see below). Accordingly, other cytotoxic agents should always be studied as "controls" before properties unique to the anthracyclines are claimed. For cardiotoxicity, the most appropriate cytotoxic control is probably actinomycin D, which intercalates with DNA with similar affinity[30] and has cell-surface-perturbating properties,[31] but does not possess dose-related cardiotoxicity.

- Because peak plasma levels rarely exceed 1 μg per ml when the drug is given by conventional methods[32-34] and because tissue concentrations are in the range of 1 to 5 μg per gram at periods of maximum uptake,[12,35] it is unlikely that effects of doxorubicin or daunorubicin at concentrations of more than 10^{-5} mol per liter have any pharmacologic meaning. Accordingly, only in vitro studies that examine effects of micromolar concentrations of anthracyclines should receive any serious attention. Indeed, because of their multiple modes of action and general cytotoxic effect, a cellular process not affected by concentrations of doxorubicin of more than 10^{-5} mol per liter would probably be reportable.

- Multiple lines of evidence point to effects on the cell membrane as being crucial to the tumoricidal and cardiotoxic actions of the anthracyclines. A doxorubicin-agarose conjugate that does not enter the cell retains full tumoricidal properties in L1210 cells,[36] and effects of doxorubicin on membrane fluidity can be correlated with relative cytotoxicity.[26] From the point of view of cardiac cells, the sarcolemma plays an extremely important regulatory role and perturbations in it may be expected to promote cellular damage.[37] Evidence that anthracyclines exert a major effect on the sarcolemma include their effects on membrane fluidity in other cells,[24-26] calcium flux,[20-22] guanylate cyclase[27] and release of vasoactive or cardioactive substances.[12,28,29] The effect of anthracyclines on intact cell membranes or on isolated membrane preparations is therefore likely to be a fertile area for future studies.

- In intact tissue anthracyclines may not act by a single mechanism, or at least not exclusively by the mechanism being investigated. There are ample data to suggest that both the tumoricidal properties and the cardiotoxicity of anthracyclines are multifactorial processes, and more attention should be given to interactive mechanisms. For example, antitumor effects may potentially involve the property of DNA intercalation,[15] cell surface properties,[24,26] stimulation of free radical synthesis[15,16] or even release of vasoactive substances.[38,39] Such multifactorial mechanisms of action may create the potential for "combination chemotherapy" within a single agent—one possible explanation for the extraordinary efficacy of this class of compounds.

There is also evidence that multifactorial processes may extend to the mechanism of cardiotoxicity, in that partial but not total protection against cardiac damage may be produced by interference with a number of putative pathogenetic mechanisms. Some of these include prevention of free radical formation,[40,41] administration of coenzyme Q_{10}[42-44] blockade of the effects of or inhibition of the release of cardiac histamine and catecholamines,[12,29] blockade of transsarcolemmal calcium flux[45] and reduction of peak plasma levels by dose-schedule modification.[6] The characteristic quality of the myocardial lesion produced by the anthracyclines[5] does not necessarily argue for a simple, singular cytotoxic site of action, but rather may be better explained by a unique interactive process involving more than one of the proposed cardiotoxic mechanisms. For example, interactive cellular mechanisms of cardiotoxicity might include alteration of the cell membrane and effects on cell surface receptors, including calcium channels; release of cardioactive substances would "summate" with anthracyclines at this locus, producing a cytotoxic increase in calcium flux. At the same time inhibition of cyclic guanosine monophosphate (GMP) synthesis might amplify adenosine 3′:5′-cyclic phosphate (cAMP)-mediated effects of anthracyclines and cardioactive hormones, stimulation of free radical synthesis would increase the membrane perturbation and inhibition of coenzyme Q_{10} would increase the sensitivity to calcium overload-mediated mitochondrial injury. Finally, inhibition of protein synthesis would then impede repair of cell damage. It should be remembered that cells are not isolated enzyme systems, nuclei or membrane preparations, but instead are the delicate interplay of a multitude of processes. In that sense the simultaneous study of multiple isolated systems or the study of intact cells or tissue may yield

more realistic results than the investigation of single, isolated systems.

Because of these complexities, continued study of the tumoricidal effects or mechanisms of drug resistance of this extraordinary class of compounds is certain to provide information of general significance in the field of cancer chemotherapy, just as the study of cardiotoxic mechanisms will continue to provide clues to the pathogenesis of other types of heart muscle disease. For these reasons and because of the paramount importance of the anthracyclines in cancer chemotherapy, we should continue to vigorously investigate the mechanism of action of these compounds with an open mind toward the ultimate conclusions.

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Case Reports

Eosinophilic Meningitis

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CEREBROSPINAL FLUID EOSINOPHILIA may be caused by a variety of agents including parasites, fungi, neoplasms and central nervous system foreign bodies.[1] Worldwide, the rat lungworm *Angiostrongylus cantonensis* is the most common cause of what is typically known as eosinophilic meningitis. Diagnosis of central nervous system infestation with this parasite in the continental United States, however, has not previously been reported. In this paper I describe a case of eosinophilic meningitis presumed to be due to *A cantonensis* that was diagnosed in Utah, review the current knowledge of human disease caused by this parasite and report two symptoms not commonly associated with this illness.

Report of a Case

A 16-year-old boy presented to the Primary Children's Medical Center, University of Utah Medical Center, Salt Lake City, because of headache, malaise, myalgia and migratory arthralgia for two weeks. For the two months before admission, the patient had been working as a field hand in Hawaii and was in good health. Two weeks before admission, headache, muscle and joint discomfort, fatigue and subjective fever developed. His temperature was 37°C (98.6°F) when seen by a local physician who suspected a viral syndrome. Symptoms increased with painful and possibly swollen ankles, knees, hands and wrists. His headache became severe. After flying to Salt Lake City from Honolulu, the patient sought medical attention.

Detailed questioning elicited that the patient, on a dare, had ingested a live land snail four weeks before admission. His medical history was remarkable only for infectious mononucleosis six months before admission.

On physical examination the patient was mildly lethargic. His temperature was 37.4°C (99.3°F), the heart rate was 100 per minute and the blood pressure was 138/82 mm of mercury. There were mild papilledema, nuchal rigidity and mild diffuse abdominal tenderness without any palpable abnormality. The hands and feet were hyperesthetic. The examination otherwise showed no abnormalities.

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The leukocyte count was 12,400 per μl with 57% polymorphonuclear cells, 31% lymphocytes, 7% monocytes and 5% eosinophils. A computed tomographic scan of the head showed normal findings. Lumbar puncture showed an opening pressure of 400 mm of water with cerebrospinal fluid that had 69 mg per dl protein, 50 mg per dl glucose, 10 erythrocytes per μl and 452 leukocytes per μl (3% polymorphonuclear cells, 63% lymphocytes, 9% monocytes and 25% eosinophils). Tests of electrolytes, renal function, liver enzymes and creatinine phosphokinase level all gave normal values. Bacterial cultures of the blood and cerebrospinal fluid were negative, and no ova or parasites were found in the stool or cerebrospinal fluid specimen. Radiographs of the ankle and chest were normal.

The patient was treated with aspirin and acetaminophen. The headache subsided some, but papilledema persisted throughout his hospital stay. His deep joint pains diminished, but his superficial skin pain and sensitivity increased after four days in hospital. Diplopia with leftward gaze, blurred vision, left facial weakness and transient hypertension to 164/80 mm of mercury developed. Then, stable with decreasing discomfort, he was discharged on the eighth hospital day.

Most of the patient's symptoms and physical findings resolved during the first few weeks following discharge. Nonetheless, some mild paresthesias are still present six months later. He has also had a pronounced bilateral decrease in visual acuity with evidence of optic atrophy.

Discussion

Angiostrongylus cantonensis is a roundworm that most commonly uses the rat as a definitive host. Snails and slugs act as intermediate hosts and carry the larvae. Larvae ingested by rats migrate to the central nervous system and finally to the rat lung where mature adult worms reproduce. Humans are an accidental final host and apparently do not allow continued reproduction.[2]

Angiostrongylus is found throughout the Pacific and southeast Asian regions of the world. Infection occurs year-round but is most common in the summer months. It has been reported in persons of all ages but, in some areas, most cases occur in children. Larvae may invade a human host either by ingestion of an intermediate host—as presumed in our patient—or following superficial skin contact with the larvae.[3]

There is no definitive diagnostic test for *A cantonensis*. On occasion, worms have been recovered from spinal fluid,[4] brain tissue[5] and the anterior chamber of the eye.[6] Usually adult worms or larvae cannot be re-

covered and the diagnosis must be based on a typical clinical presentation, spinal fluid eosinophilia and travel to or contact with an area known to host the organism.

The typical clinical course[2,7,8] begins a few days to four weeks after contact with the larvae. Headache is the most common presenting symptom and may be accompanied by signs of meningeal irritation. Fever is usually absent or low grade. Neurologic abnormalities are not uncommon and include papilledema, visual impairment, sixth and seventh cranial nerve weakness, paresthesias and altered mental state. Peripheral eosinophilia is common, and elevated cerebrospinal fluid leukocyte counts, with many eosinophils (average of 40%), are usual. The clinical course is usually self-limited, with symptoms resolving in one to five weeks. Facial paralysis is often the most persistent symptom.

There is no known specific therapy, and supportive measures are the indicated treatment. Antibiotics and steroids are ineffective.[7] The illness is usually benign, and the prognosis for gradual and full improvement within one to two months is good.[7]

This patient ingested a possible intermediate host from an area endemic for *Angiostrongylus*. His course of headache, central nervous system involvement, spinal fluid eosinophilia and some gradual resolution is characteristic of *A cantonensis* infestation. His myalgia and arthralgia, however, were unusual. Laboratory tests in search of evidence for myositis, active mononucleosis and rheumatic fever gave normal findings, and it was concluded that the myalgia and arthralgia were caused by his parasitic disease. The duration of visual impairment seen in this patient is also unusual. Possible pathogenetic mechanisms of altered vision include optic neuritis and intracranial adhesions and are discussed elsewhere.[7]

In conclusion, this patient shows characteristic findings of the eosinophilic meningitis caused by *Angiostrongylus cantonensis* along with newly associated symptoms. With frequent travel to and from endemic areas, it behooves physicians all over the world to be aware of this disease.

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Effect of Respiratory Alkalosis in Tricyclic Antidepressant Overdose

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OVERDOSAGE WITH TRICYCLIC ANTIDEPRESSANTS is a common clinical problem. Patients may present with signs and symptoms of peripheral (tachycardia, mydriasis, dry mouth, ileus) or central (agitation, delirium, seizures, coma) cholinergic blockade.[1,2] The most life-threatening consequence of overdosage from these drugs may include a variety of cardiac conduction and rhythm disturbances.[2-8] Treatment of tricyclic antidepressant-induced cardiotoxicity with physostigmine and various antiarrhythmic drugs has yielded conflicting results.[2,7-9] Resolution of cardiac conduction and rhythm disturbances following systemic alkalinization has been reported in experimental animals poisoned with tricyclic antidepressants[9,10] and in human subjects.[10-13] Alkalinization has generally been accomplished with sodium bicarbonate and occasionally with hyperventilation. Previous clinical reports attesting to the beneficial effects of systemic alkalinization, however, have involved subjects who were acidemic before treatment, and it has been argued that their improvement was the result of correction of the accompanying acidemia and not the alkalinization per se.[14]

The following case report suggests that tricyclic antidepressant-induced alterations in cardiac conduction can be significantly affected by hyperventilation and respiratory alkalosis in the absence of pretreatment acidemia.

Report of a Case

A 30-year-old woman was admitted to the emergency department after being found unconscious by her family. The patient had a history of depression and attempted suicide and was receiving outpatient psychiatric care. The patient's family was aware that she was taking medications, but was uncertain of the kind or amount.

Initially her temperature was 41.0°C (105.8°F), pulse 128 per minute and regular, respirations 20 and blood pressure 90/60 mm of mercury. The patient was comatose and unresponsive to verbal or tactile (painful) stimuli. On neurologic examination she had no oculocephalic, oculovestibular, corneal or gag reflex. Both pupils measured 4 mm and were weakly reactive to light. The extremities were flaccid and areflexic. The

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rest of the general physical examination showed only dry, warm skin and absent bowel sounds.

Laboratory studies done on admission showed normal serum electrolyte values except for a serum bicarbonate of 20 mEq per liter (normal 24 to 34). Arterial blood gas determinations done while the patient was spontaneously breathing room air showed an oxygen partial pressure (Po_2) of 69 mm of mercury, carbon dioxide partial pressure (Pco_2) of 31 mm of mercury and pH of 7.44. The electrocardiogram (EKG) (Figure 1) showed a regular tachycardia with wide, bizarre QRS complexes and right axis deviation.

Figure 1.—The initial 12-lead electrocardiogram shows sinus tachycardia and an extremely prolonged QRS duration (200 msec) and QT interval (corrected QT, 544 msec). The mean frontal plane QRS axis is +270 degrees. The arterial pH is 7.44.

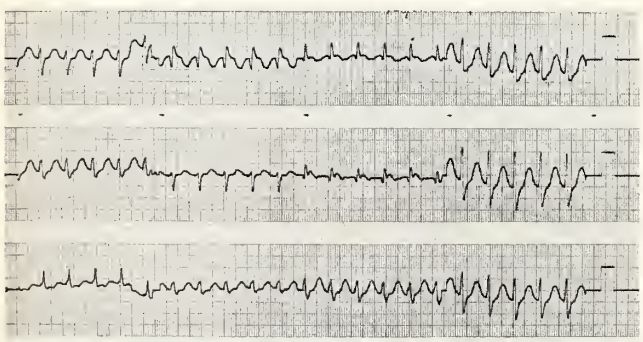

Figure 2.—A 12-lead electrocardiogram done after mechanical hyperventilation (arterial pH, 7.65). The QRS duration and corrected QT interval are 140 and 527 msec, respectively. The mean frontal plane QRS axis is +140 degrees.

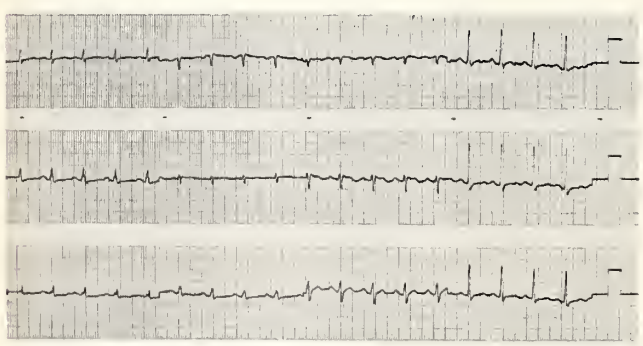

Figure 3.—Electrocardiogram done at the time of discharge. QRS duration (95 msec), corrected QT interval (427 msec) and QRS axis (+50 degrees) are all within normal limits.

While in the emergency department, the patient's blood pressure gradually fell to 70/50 mm of mercury despite the administration of one liter of normal saline solution. An infusion of dopamine hydrochloride solution was begun, initially at 5 μg per kg a minute and rapidly increased to 15 μg per kg a minute. Because the clinical and electrocardiographic findings suggested tricyclic antidepressant overdose, the patient was given 2 mg of physostigmine intravenously but no change in vital signs, mental state, heart rate or rhythm was noted. About 40 minutes after the dopamine therapy was started, pulseless ventricular tachycardia developed, which responded to the second of two precordial blows with reversion to the original rhythm. The patient was then intubated and mechanically hyperventilated with 100% oxygen on a pressure-cycled respirator. Over the next 20 minutes, the blood pressure gradually rose to 100/70 mm of mercury. Arterial blood gas determinations 20 minutes after initiating hyperventilation showed a Po_2 of 689 mm of mercury, Pco_2 of 14 mm of mercury and pH of 7.65. A second EKG done at this time (Figure 2) showed a sinus tachycardia with significant narrowing of the QRS complex.

The patient's family returned to the emergency department and reported that they had found two empty pill bottles at her home: amitriptyline hydrochloride, 50-mg tablets (100 dispensed), and flurazepam hydrochloride, 30-mg tablets (60 dispensed). A partially empty bottle of acetaminophen with 60 mg of codeine was also found. All medicines had been prescribed within the preceding seven days.

The patient was admitted to the intensive care unit and treated with supportive measures, and 36 hours after admission she responded to verbal commands. Vital signs, mental state and electrocardiographic findings gradually returned to normal, and the patient was discharged after an uncomplicated five-day stay. An EKG done on the day of discharge showed normal atrioventricular and intraventricular conduction (Figure 3).

Discussion

This patient had the classic findings seen in tricyclic antidepressant overdose: anticholinergic and cardiac toxic reactions and hypotension.[1-8] The nature of the ingestion was confirmed by finding an empty bottle of amitriptyline at the patient's home, and later by her own admission. The other drugs found at the scene (especially flurazepam and codeine) undoubtedly depressed her mental state and probably explain the failure of the mental state to improve after administration of physostigmine.[15] None of these other drugs, however, has significant cardiotoxicity,[16] and the cardiotoxic effects seen in this patient are entirely consistent with the effects of tricyclic antidepressants on the myocardium.[1-8]

The tricyclic antidepressants at toxic serum concentrations may produce cardiac dysrhythmias or altered

cardiac conduction (or both). Sinus tachycardia and some supraventricular rhythm disturbances have been ascribed to the anticholinergic effects of this class of drugs.[1,2,7,8] Conduction disturbances and most ventricular dysrhythmias, however, are thought to be the result of a direct effect of tricyclic antidepressants on the myocardium ("membrane-stabilizing" or "quinidine-like" effect).[2-5,7,8] Conduction delay has been shown electrophysiologically to occur below the bundle of His and within the specialized conduction system of the ventricular myocardium.[3,7,17]

At present there is no accepted, standard therapy for the treatment of tricyclic antidepressant-induced dysrhythmias and conduction disturbances. Physostigmine has been reported to be of value, but strong evidence supporting its efficacy is lacking.[7-9,18] Most reports of a favorable response to physostigmine are limited to the treatment of supraventricular rhythm disturbances. Therapy with various antiarrhythmic drugs has yielded similar inconsistent benefits and frequent untoward side effects.[2,9]

The value of systemic alkalinization in the management of rhythm and conduction disturbances produced by tricyclic antidepressants has been reported.[9-13] Brown and co-workers showed in experimental animals that amitriptyline-induced dysrhythmias resolved when the arterial pH was increased with hyperventilation or intravenous administration of sodium bicarbonate.[9,10] Recent case reports attest to the efficacy of this modality in human subjects.[10-13] In a comprehensive review of tricyclic antidepressant overdosage, Callaham stated that alkalinization is effective in the treatment of most forms of cardiotoxic reaction to tricyclic antidepressants.[2] However, prior reports are limited to experimental animals or patients who were acidemic before treatment, and it is unclear whether cardiac state improved because of correction of acidemia or because of pH change per se.[14]

There is evidence to support the concept that any increase in pH should be of benefit in the management of tricyclic antidepressant-induced cardiotoxicity. At physiologic pH, the drugs are more than 90% bound to plasma proteins.[10,19] Because only free (unbound) drug is pharmacologically active, increasing tricyclic antidepressant binding to plasma proteins should make less drug available to tissues, including the myocardium. Only a small fraction of the total amount of drug in plasma is unbound; therefore, increasing protein binding by a small percentage will produce a large decrease in the proportion of free drug. Brown and colleagues have shown that plasma protein binding of amitriptyline increases from 82% at a pH of 6.7 to 98% at a pH of 7.5.[10] This corresponds to a ninefold decrease in the free and potentially toxic drug concentration. In a more physiologic pH range, an increase from 7.3 to 7.5 was shown to increase protein binding from 96% to 98%, thus halving the proportion of free drug.[10]

The patient was not acidemic (pH 7.44), but showed greatly improved intraventricular conduction after the induction of respiratory alkalosis (Figures 1 and 2). The second EKG was recorded only 1½ hours after the first; any significant decrease in plasma tricyclic antidepressant concentration produced by metabolism and excretion would not be expected within this time span.[2,6,20] The patient received physostigmine 60 minutes before the second EKG, but any parasympathomimetic effect would have waned during this time interval.[1] Dopamine at the rate administered would not be expected to affect intraventricular conduction but may have facilitated the induction of ventricular tachycardia.[21] It is our contention that the improvement in intraventricular conduction was directly attributable to induced respiratory alkalosis.

Improved cardiac conduction produced by alkalinization (in the presence or absence of acidemia) may have important clinical implications. Delayed conduction predisposes the heart to malignant ventricular dysrhythmias which may be of reentrant origin.[22] Improved His-Purkinje conduction may prevent the development of ventricular dysrhythmias, aid in the conversion to a normal sinus mechanism or prevent dysrhythmia recurrence (or all three). Systemic alkalinization produced by respiratory means has advantages over parenteral sodium bicarbonate therapy. Respiratory alkalosis can be induced and terminated rapidly, and a predetermined P_{CO_2} and pH may be attained if the ratio of dead space to tidal volume can be estimated and the minute ventilation adjusted accordingly. Respiratory alkalosis is not associated with the sodium and osmolar "load" and the relative unpredictability of pH change that attends sodium bicarbonate administration.

Induced pronounced hypocapnia is not free of potential adverse effects. These include electrolyte shifts, decreased ionized calcium level, leftward shift of the oxyhemoglobin dissociation curve, decreased cerebral blood flow and occasionally induction of dysrhythmias.[23] When this modality is used in a setting of tricyclic antidepressant overdose, arterial blood gases must be carefully monitored; a pH greater than 7.60[24] or a P_{CO_2} of less than 20 mm of mercury[25] is probably undesirable.

When used with the proper caution, the clinical benefits of induced respiratory alkalosis may be substantial. These benefits may lend themselves not only to the therapeutic use of this modality in treating tricyclic antidepressant-induced cardiotoxic reaction but also to its "prophylactic" use in preventing dysrhythmias in patients with significant overdoses.

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Polymicrobial Septicemia After Liver Biopsy

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NEEDLE BIOPSY of the liver engenders minimal risk to patients when the procedure is expertly done. In Lindner's series of 123,000 biopsies, the death and morbidity rates were only 0.015% and 0.29%, respectively.[1] Although a variety of complications may follow liver biopsy,[2,3] serious infection rarely occurs. We report an unusual case of polymicrobial septicemia after percutaneous liver biopsy and summarize the pertinent literature.

Report of a Case

A 73-year-old man was admitted to Martin Luther King, Jr/Charles R. Drew Medical Center (Los Angeles) because of yellow eyes and dark urine for two months and pruritus for two weeks. He had no nausea, vomiting, abdominal pain, fever or recent weight change. There was no history of alcohol abuse, exposure to hepatotoxins, previous hepatitis or blood transfusion. He had undergone a cholecystectomy ten years before. On physical examination he appeared comfortable and had normal temperature and blood pressure. The liver span on percussion was 15 cm and the edge was firm, smooth and slightly tender. There were no other abnormal findings.

Laboratory studies at the time of admission gave the following values: hemoglobin, 12.5 grams per dl; hematocrit, 38.6%; leukocyte count, 9,600 per μl, with normal differential, and platelet count, 216,000 per μl. The urine contained bile. The serum glucose, blood urea nitrogen, electrolytes and amylase levels were normal. The total bilirubin was 4.6 mg per dl (direct, 2.4 mg per dl); serum aspartate amino transferase (AST, or SGOT), 212 IU (normal 8 to 30); serum alanine amino transferase (ALT, or SGPT), 348 IU (normal 3 to 36); alkaline phosphatase, 216 IU per liter (normal 25 to 97); total protein, 6.5 grams per dl; albumin, 3.5 grams per dl; prothrombin time, 10.4 seconds (control 10.4), and partial thromboplastin time, 27 seconds (control 31). Tests for hepatitis B surface antigen, surface antibody and core antibody were negative, as were those for hepatitis A antibody and antinuclear antibody. Results of chest and abdominal roentgenograms, abdominal ultrasound, a liver-spleen scan with technetium Tc 99m and an electrocardiogram were normal.

Because of a question of intrahepatic cholestasis, a liver biopsy was done on the fourth hospital day using a TruCut needle. The biopsy needle was inserted through the right eighth intercostal space in the midclavicular line and two passes were made into the liver. The liver biopsy specimen showed inflammation of portal tracts with adjacent necrosis and bile cholestasis, suggesting mild chronic hepatitis. About eight hours later, the patient had a shaking chill and his temperature rose to 39°C (102.4°F). The leukocyte count was 14,600 per μl with a leftward shift. Results of urine analysis, urine culture and chest x-ray study were all normal. However, the following two Gram-negative bacilli were cultured from the blood: *Klebsiella oxytoca,* sensitive to gentamicin, tobramycin, amikacin, cephalothin, cefoxitin, chloramphenicol and trimethoprim-sulfamethoxazole but resistant to ampicillin, carbenicillin and tetracycline; and *Escherichia coli,* sensitive to all aforementioned antibiotics.

Therapy with gentamicin sulfate, 80 mg given intravenously every eight hours, was started on the sixth hospital day. The patient's temperature continued to rise to 38°C to 39°C (101°F to 103°F) each day. Repeat laboratory studies showed a total bilirubin of

Refer to: Dhawan VK, Thadepalli H, Ulmer DD, et al: Infectious polymicrobial septicemia after liver biopsy. West J Med 1983 Sep; 139: 376-378.

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19 mg per dl (direct, 8.8 mg per dl); AST, 41 IU; ALT, 111 IU, and alkaline phosphatase, 805 IU per liter. Findings of an abdominal ultrasound examination on the ninth hospital day were again normal. Hepatobiliary imaging with technetium Tc 99m diisopropyl iminodiacetic acid on the same day, however, showed possible narrowing of the common bile duct. A blood culture obtained on the tenth hospital day again showed *E coli* with unchanged antibiotic sensitivities. Cefoxitin sodium, 2 grams intravenously every six hours, was administered along with gentamicin. A body scan using gallium citrate Ga 67 showed no unusual uptake.

On the 14th hospital day an exploratory laparotomy was done. A collection of about 20 ml of hemorrhagic fluid was noted under the capsule of the liver at the site of the liver biopsy but the rest of the liver surface appeared normal. The fluid was sterile to culture. Results of an intraoperative cholangiogram ruled out biliary obstruction. A wedge biopsy specimen of the liver again showed mild chronic hepatitis. The postoperative course was uneventful and the patient remained afebrile. He continued to receive cefoxitin and gentamicin for 14 additional days, his jaundice slowly decreased and he improved progressively. Blood cultures on the 16th hospital day and subsequently were negative. The patient was discharged well on the 31st hospital day and was asymptomatic at the time of follow-up a month later.

Discussion

The liver, containing about 60% of the entire reticuloendothelial system, plays a major role in defense against bacterial invasion and sequesters bowel organisms with high efficiency.[4] Whereas bacteria can be cultured from the portal vein at operation in up to a third of patients, peripheral blood specimens cultured simultaneously are uniformly sterile.[5] In cirrhosis, spontaneous bacteremia may occur due to altered structure and blood flow.[6]

Despite the fact that hepatic macrophages often contain bowel organisms, infections complicating needle biopsy are remarkably rare. Transient bacteremia consequent to this procedure, however, does occur with some frequency. Le Frock and co-workers, who obtained blood cultures from 89 patients before and 5, 10, 15 and 30 minutes after liver biopsy,[7] found transient bacteremia in 12 (13.5%). The organisms cultured included *E coli, Klebsiella, Bacteroides, Enterococcus, Diphtheroides, Staphylococcus aureus,* α-hemolytic streptococcus and *Streptococcus pneumoniae.* In five of these patients, the same organism was found in blood and in the liver biopsy material, supporting the view that bacteria from the liver entered the bloodstream. Notably, all patients remained symptomatic. Other investigators have also found transient bacteremia after liver biopsy but with lesser frequency and usually involving patients compromised by hepatitis and receiving immunosuppressive therapy.[8-10]

Although bacteremia after liver biopsy is not infrequent, septicemia is distinctly unusual. Reported cases are summarized in Table 1. All patients were 58 years or older and all except one were men. Causative organisms mirror the bowel flora, with *E coli* being the most frequent offender. *K oxytoca* septicemia following liver biopsy is reported for the first time in the present case.

There are only two previous reports of polymicrobial septicemia following liver biopsy. In one (case 1

TABLE 1.—*Report of 8 Cases of Septicemia Following Liver Biopsy**

Case, Age, Sex	Liver Biopsy Diagnosis	Causative Organisms	Type of Needle	Therapy	Outcome	Reference
1 68 ♂	Subacute pericholangitis	*Escherichia coli* and *Streptococcus viridans*	Not reported	Penicillin and gentamicin; refused surgical procedure	Improved; lost to follow-up	LoIudice et al[11]
2 79 ♂	Chronic cholangitis with secondary biliary cirrhosis	*E coli*	Not reported	Ampicillin; cholecystectomy	Resolved	LoIudice et al[11]
3 58 ♂	Cirrhosis and carcinoma of liver	*E coli*	Not reported	Gentamicin	Died; had right subdiaphragmatic abscess	LoIudice et al[11]
4 79 ♀	Normal liver	*E coli*	Menghini	Gentamicin, then ampicillin	Resolved	Murray and Dugowson[12]
5 58 ♂	Chronic cholangitis	*E coli*	TruCut	Gentamicin; operation to remove villous adenoma of ampulla of Vater	Resolved	Navarro et al[13]
6 58 ♂	Typhoid hepatitis	*Salmonella*	Menghini	Chloramphenicol	Resolved	Singh et al[14]
7 68 ♂	Portal fibrosis, chronic cholangitis	*E coli* and *Bacteroides fragilis*	Vim-Silverman	Ampicillin and gentamicin, then changed to cefazolin and gentamicin and chloramphenicol; refused surgical procedure	Resolved	Moreira Vicente et al[15]
8 73 ♂	Chronic hepatitis	*E coli* and *Klebsiella oxytoca*	TruCut	Gentamicin and cefoxitin	Resolved	Present case

*Another case of possible septicemia involving *Clostridium welchii (Clostridium perfringens)* was reported but no details were given (Morris et al[16]).

in the table), *E coli* and *Streptococcus viridans* were found[11] and in the other (case 7) *E coli and Bacteroides fragilis*.[15] In the latter, a small intestinal perforation could not be excluded, a condition not evident in our case.

With the exception of one patient (case 4), all previously reported cases had an identifiable source of septicemia such as subdiaphragmatic abscess or cholecystitis. In our patient no such foci of infection were identifiable; hence, this constitutes the second report of a de novo septicemia following liver biopsy and the first such instance of polymicrobial infection.

The abrupt onset of fever, chills and leukocytosis within eight hours of the biopsy strongly suggested an infectious process in our patient. Because strict asepsis was observed during the procedure and no other source of infection was discerned after a meticulous search, including laparotomy, we speculate that bacteria sequestered in hepatic macrophages were introduced into the bloodstream by the biopsy. A complex interaction of a subcapsular hematoma, microorganisms and the host defenses then favored the development of septicemia.

Two cases of serious infection other than septicemia following liver biopsy have been reported. Klein and associates reported the development of a liver abscess in a 47-year-old man who had undergone liver biopsy with a Menghini needle a month before.[17] Schnyder and colleagues reported peritonitis occurring after needle biopsy of the liver in a patient who had a liver abscess.[18]

The development of fever shortly after a liver biopsy should suggest the possibility of septicemia and therapy should be initiated promptly. Because the vast majority of organisms causing sepsis under this circumstance are coliform aerobic bacilli, antibiotic therapy should be directed empirically against such bacteria. Use of an aminoglycoside with a cephalosporin would appear most appropriate until the reports of blood culture become available. Prognosis appears to be excellent in most cases. A surgical procedure should be done to relieve biliary obstruction if present.

Because transient bacteremia after liver biopsy is not unusual, the question arises as to the need for antibiotic prophylaxis for patients with structural abnormalities of the heart valves and vascular prostheses. No objective data are available to answer this question. However, because bacteremia following liver biopsy is most commonly due to aerobic Gram-negative bacilli and because these organisms are infrequent causes of endocarditis, routine use of toxic agents such as aminoglycosides are not warranted.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Costs of Laminar Air Flow Hospital Rooms

TO THE EDITOR: I read with interest the speciality conference "Preventing Infection in Neutropenic Cancer Patients" by Beutler, Barth and Bayer[1] in the May issue. I am curious to know how the stated cost of $120,000 per unit for laminar air flow rooms was arrived at that is quoted on page 695.

We have 16 laminar air flow units at the Fred Hutchinson Cancer Research Center, Seattle, and are installing an additional 20 units. The total cost of these units (installed) in a regular hospital room is currently $31,000. Did the estimated cost of $120,000 include the cost of building a conventional hospital room plus the added cost for the laminar air flow equipment? If so this is a misleading figure as the choice one faces is the cost differential between a conventional hospital room and a laminar air flow room and not the cost differential between a laminar air flow room and no room at all. For readers unfamiliar with laminar air flow rooms the quoted price of such a facility is frightening enough to discourage further consideration of this modality of infection prophylaxis. In fact, the cost of putting laminar air flow rooms in a newly constructed building is such a small fraction of the total cost that it is not a serious limitation.

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REFERENCE

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* * *

Dr Barth Responds

TO THE EDITOR: In reply to Dr Buckner's letter, the figure of $120,000 per unit is a composite figure derived from several sources and includes both direct and indirect costs.

I agree with Dr Buckner that the cost of a single semiportable laminar air flow room to fit in a typical two-bed ward room constructed to Hill-Burton standards is approximately $31,000. As mentioned by Pizzo[1,2] room preparation for laminar air flow unit installation, exclusive of major reconstruction, adds another $5,000 to $8,000. In addition to the establishment cost of just the physical plant mentioned above, one must include, for the typical nonuniversity teaching hospital, the establishment or expansion costs for a sterile kitchen, sterile supply service, microbiology laboratory and nursing education, as well as cost incurred for training dietary, housekeeping and maintenance personnel.

In informal discussions with various Los Angeles County building contractors, laboratory supervisors, dieticians, nursing and hospital administrators, the initial expenditure was $60,000 to $70,000. There is no question that the cost per unit would decrease once the initial capital expenditures for many of these items were made; nonetheless, they are costs that need to be considered.

I would like to add one additional thought that needs to be considered. Most of these units are being installed in existing two-bed ward rooms. When this is done, one should consider in the overall cost of such a unit the potential of lost revenue from one less hospital ward bed per unit which, when calculated at the typical 75% occupancy rate at $250 a day, equals $68,437.50 a year in lost revenue. Furthermore the occupancy rate of laminar air flow rooms in several busy 500-plus-bed community hospitals with active oncology programs is only 35% to 50%.

In short, the cost of laminar air flow rooms is significant, whether it is $30,000 per unit or $120,000 per unit. The cost needs to be weighed institution by institution in light of the efficiency of such units in producing the desired results, the utilization of this medical technology by hospital staff and the increasing trend toward cost-conscious/cost-effective medicine.

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Compliance

TO THE EDITOR: Patient compliance in taking medicine has been a problem for the medical profession for years. My recent experience, however, seems to be a new variation.

I was caring for a 74-year-old man for moderate

hypertension. He was very cooperative. He filled his prescriptions and complied with all instructions. Whenever his blood pressure rose or a modification in therapy was needed, he changed his medications and management as prescribed. He never complained. He was an ideal patient. This continued for five years. I attended him regularly on a monthly basis. His wife, who usually accompanied him on these visits, was content.

About five years later I was called to see his wife at their home. Glancing about I saw an open closet with shelves filled with prescription bottles. On inspection, I found every medicine I ever prescribed for the five years I treated her husband. Each bottle was filled, just as it had come from the pharmacy. Every prescription I ever prescribed had been filled, but never touched. The patient had had every prescription refilled whenever it was due. He had kept tab whenever a refill was necessary.

When questioned as to this deceit, he stated he wanted to keep me happy.

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Who Was Sir William Osler?

To the Editor: Professor Geyman's proposal[1] in the June issue to revive the Oslerian tradition depends on knowledge of the tradition, a subject that I began to investigate in 1962 at the University of Rochester by quizzing interns and residents. The study was suspended in 1966 during postgraduate study in London, then resumed in 1967 at Pacific Medical Center in San Francisco, where we see interns and residents from a broad range of US medical schools. Lectureships at other institutions made possible inclusion of some of those house staff. Over 400 have responded.

As a neurologist, my own interests in the Oslerian tradition are both broader and narrower than Geyman's. The survey consisted of three questions:

1. *Who was Sir William Osler?* (A correct answer included knowledge of his famous textbook of medicine, or of his role in the founding of the medical school at Johns Hopkins, or of his later career at Oxford. Any knowledge in just one of these areas was considered a passing answer.)

2. *Who was Harvey Cushing?* (A passing answer included knowledge that Cushing was a pioneer in American neurosurgery, or some knowledge of his contributions in hypothalamic-pituitary disorders, or merely knowledge of his prize-winning biography of Osler.[2] Answers such as "He was a famous endocrinologist" were not acceptable.)

3. *Who was John Fulton?* (Correct answers included knowledge of Fulton's editions of Howell's *Textbook of Physiology*, or any knowledge of Fulton's contributions to neurophysiology, or merely knowledge of Fulton's prizewinning biography of Cushing.[3])

In this study, largely of United States citizens and graduates of many of our leading medical schools and universities, only three participants were able to meet the criteria for identification of Osler; two of these and only one other were able to identify Cushing; none of the participants identified Fulton. Faculty were not invited to participate, but I would be interested in Professor Geyman's score, since his bibliography[1] does not include the Cushing biography of Osler.

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Comment on Ethical Crises and Cultural Differences

To the Editor: The article "Ethical Crises and Cultural Differences"[1] is made especially interesting by the authors' conclusions concerning the hazards of stereotyping and generalizations. Some points, however, merit more consideration in view of the purpose of the article.

The case study, for instance, seems more Egyptian than Arab; the assumption of homogeneity among Arabs, and the emphasis on the "core of Arabism," can lead to some misunderstandings. Also, Drs Meleis and Jonsen projected a subjective "reading" of a case amenable to several interpretations. The authors point out that probing medical questions are often viewed by Arab-American patients as unnecessary and intrusive, and hence undermine the patient-doctor trust. To an Arab patient, though, fewer questions are not an indication of either better care or a more competent physician. My experience with Egyptian, Kuwaiti, Saudi, Palestinian, Syrian and Sudanese patients indicates that questions tend to put patients at ease and are a direct correlate of a physician's concern.

Indeed, Arab patients take issue neither with excessive questioning in itself nor with its subject-matter; the problem usually resides in the phrasing of the questions, which can make clinically pertinent inquiries seem irrelevant and insulting. A case in point is asking the pious Mr Ahmed about his liquor consumption, or questioning a single girl as to her use of contraceptives, or inquiring whether a male patient is homosexual. If any of these questions are too blatantly put, they are unacceptable to an Arab patient and will undercut his or her respect for the physician. The necessary inquiries can be tactfully and privately posed, so as not to insult the patient.

After tactful inquiry and providing the necessary information to the patient, there is still the issue of consent. The article stresses patient consent as a pillar of Western values applied to medicine—patient autonomy, individual freedom and the like. The stress on patient consent, though, cannot claim such noble origins. Rather, it has proliferated with the malpractice suit and reflects definite shortcomings in confidence, trust and integrity in the doctor-patient relationship.

The shortcomings are much more a Western than a European phenomenon, and it is for this reason that a request for consent would sound irrelevant to Mr Ahmed and a sign that his doctor neither trusts him nor is worthy of his trust. Had Mr Ahmed been approached from the view that consent is "routine" for the protection of doctor, patient and hospital, he probably would have signed gracefully. In my judgment, this applies to all patients from countries where legal prophylaxis does not accompany medical practice. In the Arab countries, patients do not sue their doctors because they trust their sincerity and view them only as tools of God. Only with the most flagrant negligence can this trust be undermined.

Subjectivity, then, when taken to extremes can become bias, as is evident in the authors' assessment of the options available to patients in the United States versus elsewhere. As long as the science of medicine is reasonably uniform, no gulf of options exists between here and the Gulf.

Similar biases, which undermine the article's quest for enhanced understanding, involve a cultural differentiation of the view of deceit—that it is reprehensible here but not so elsewhere. The deceit discussed is in relation to provision of information to the patient. Here, though, honesty is confused with bluntness. The difference between American and Arab patients and physicians is not in the amount of information provided or withheld but in the methodology of communication.

As physicians, we should admit to ourselves that we deal in probability rather than absolute truths; if this fact alone is remembered, it changes the tone of communication between patients and doctors, be they Arabs or Anglo-Saxons. When, for instance, we are informing a patient of a fatal disease, we should recall the spontaneously cured cases of hypernephromas in the literature (three in 1978), and the rare cases of lung cancer that improve, or the patients whom we have followed up for four to six years after they have been given four to six months on probabilistic terms. It is these considerations—a refusal to shut hope's door—that most differentiates the manner of an Arab from an American physician, rather than the former's alacrity to deceit.

Another point of contention with the authors relates to their assessment of the role of the patient's family. Certainly, an Arab family may seem more attached to the patient and more emotional about the medical goings on. This does not, though, indicate an inability to prepare for death on their part. In my experience, once word is passed that a case is critical, the family goes behind closed doors to make their preparations, incorporating the full spectrum of details from funeral arrangements to outstanding debts.

The issue of death, it must be pointed out, is cast differently between Egyptians and non-Egyptian Arabs. The latter tend to accept death matter-of-factly. Egyptians, however, have behind them a 7,000-year culture built on attempts to defy death and achieve immortality; hence their acceptance of death is more limited, and the grief more open.

In general, death in the Middle East is viewed more fatalistically than in the West—as the will of God. This naturally tends to make Arabs more reticent about death; this silence is an expression of long-held beliefs about life and death, common to all Moslems as expressed by the saying related to the Prophet: "Work in the present as if you will live forever, and work for the hereafter as if you will die tomorrow."

Finally, a last comment about bringing a "Moslem Sheikh" to the bedside of the sick patient was most unfortunate. It expressed bringing a layman to a professional technological situation and is a declaration of bankruptcy of the medical institution; most of these people believe in healing through medicine (teachings of the Prophet to seek medicine and medical advice for any sickness) not through the influence of prayer.

In Islam there is no clergy, so even from the religious point of view his presence looks both irrelevant and ominous. In my judgment it would have been more productive in this case to find an Egyptian physician who belonged to the same religion and spoke the same language to help bridge the gap that I think was easily bridgeable.

This valuable article, meant to bring people closer together and to create a common understanding, might unwittingly be counterproductive if we don't emphasize that kindness, sympathy and love are elements of a universal language, and these elements will work only if they are felt and made real. Human beings at a time of suffering and need will feel and appreciate the sincerity of those who care for them.

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Correction: Arsenic Poisoning

AN ERROR OCCURRED in the case report by Selzer and Ancel on chronic arsenic poisoning in the August issue (Selzer PM, Ancel MA: Chronic arsenic poisoning masquerading as pernicious anemia. West J Med 1983 Aug; 139:219-220). In the Discussion section on page 220, the third sentence should read as follows: "In *arsenic poisoning,* the erythrocytes are primarily normocytic and normochromic, and basophilic stippling is common; hypersegmented neutrophils are absent or rare, and relative eosinophilia may be seen." —THE EDITORS

Topics in Primary Care Medicine

Common Ectoparasites

FRANCIS D. PIEN, MD, *and* JAY L. GREKIN, MD, *Honolulu*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The management of ectoparasite infestation is important in office practice to general medicine practitioners. There is currently a "pandemic" of scabies which is becoming more common among all age groups and socioeconomic classes. Scabies has become a venereal disease in sexually active adults as well as a nosocomial infection within hospitals. Pediculosis (lice) is an age-old problem, especially in times of warfare and in the presence of poor hygiene and sexual permissiveness. Furthermore, body lice have in the past transmitted such diseases as epidemic typhus *(Rickettsia prowazekii),* trench fever *(Rickettsia quintana)* and epidemic relapsing fever *(Borrelia recurrentis).*

Scabies

Parasite

Scabies is a skin infestation by the mite, *Sarcoptes scabiei* (Figure 1). The adult mite has four pairs of legs, two anterior and two posterior. The four front legs end in suckers and the rear legs end with long trailing bristles. Protruding from the front of the organism are mouth parts. The adult female is the most commonly found mite in scabies. It enters the human skin and burrows into the stratum corneum, residing just below its surface and laying two to three eggs per day during a lifetime of about 30 days. These eggs hatch giving rise to larvae which molt to produce nymphs. The nymph molts two more times before becoming an adult mite. This whole process takes approximately ten days. The young female copulates with a male mite, then enlarges and enters the stratum corneum.

Clinic Presentation and Diagnosis

Pruritus is the most common clinical manifestation in scabies, especially at night. Since scabies is an immunologic response to the organism, the symptoms and rash may develop over four to six weeks. The most frequent lesions are papulovesicular, though the classic finding is a burrow, produced by the mite burrowing within the stratum corneum. Frequently these lesions are excoriated and even impetiginized. The most common areas of involvement are hands, fingerwebs, flexor surfaces of the wrists, extensor areas of the elbows and knees, axillae, periumbilical area, breasts, genitalia (particularly the penis and scrotum) and buttocks (Figures 2 and 3). The mite rarely affects any area above the neck in adults. In bedridden patients, scabies may be limited to skin sites in direct contact with sheets. "Nodular scabies" is caused by a hypersensitivity reaction to the mite. These nodules can persist for months despite effective antiscabietic therapy. Nodules are most commonly seen in the crural area and axillae and on genitalia.

Crusted or keratotic scabies, formerly known as "Norwegian scabies," occurs in immunocompromised patients. These patients present with thick, hyperkeratotic areas on the palms, soles, elbows and knees, with involvement of head and neck areas as well. This form of scabies is highly contagious because of the large numbers of mites found on the skin. Crusted scabies is rare and may go undiagnosed for a prolonged period of time, allowing multiple contacts to become infested.

Scabies is usually transmitted by direct contact with infected persons. School children may introduce the

Refer to: Pien FD, Grekin JL: Common ectoparasites (Topics in Primary Care Medicine). West J Med 1983 Sep; 139:382-385.
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disease into their own households. Scabies is probably spread infrequently by fomites because only a small number of mites are shed by a patient and mites do not survive longer than two to ten days without attaching to human skin.

Diagnosis

The diagnosis of scabies is made by both physical examination and identification of the mite. Because the lesions are pleomorphic and may be excoriated, eczematized and impetiginized, one must keep a high degree of suspicion. Differential diagnosis includes insect bites, impetigo, neurodermatitis, lichen simplex chronicus and dermatitis herpetiformis. The mite can be identified by shaving a lesion with either a #15 blade scalpel or a razor blade. The material is then placed on a slide under mineral oil or 10% or 20% potassium hydroxide solution, and a cover slip. The specimen is examined under a microscope for the mite, eggs or fecal pellets. A skin biopsy may be helpful in atypical cases or in lesions not diagnosed by skin scraping.

Treatment

The treatment of scabies is somewhat controversial. Most authorities advise the single application of 1% gamma benzene hexachloride (Kwell) lotion or cream.[2] Gamma benzene hexachloride is left on the skin for approximately 8 to 12 hours before it is washed off. Kwell should be applied thinly and evenly, and used on the neck and head only if there is evidence of scabies in these areas. This drug has been associated with central nervous system toxicity, but most cases have represented a misuse of the preparation. Absorption of 1% Kwell may, however, be increased in severe cases of scabies with widespread excoriation or secondary infection. In infants and pregnant women, some physicians prefer crotamiton (Eurax). This drug also has antipruritic properties but is less effective than Kwell and requires a second application 24 hours later. A preparation of 5% precipitated sulfur in petrolatum can also be used to treat young children; adults can be treated with the 10% concentrated sulfur.

It is wise to treat close contacts of an infected person, such as family members, even if they are asymptomatic. Patients should wash with hot water their bedding, towels and clothing worn over the past two days. It is usually not necessary to clean outer garments or furniture. The patient should be instructed that even though the mites and eggs are killed by therapy, itching and some lesions may persist for several days or even weeks.

Topical use of corticosteroids is necessary to treat

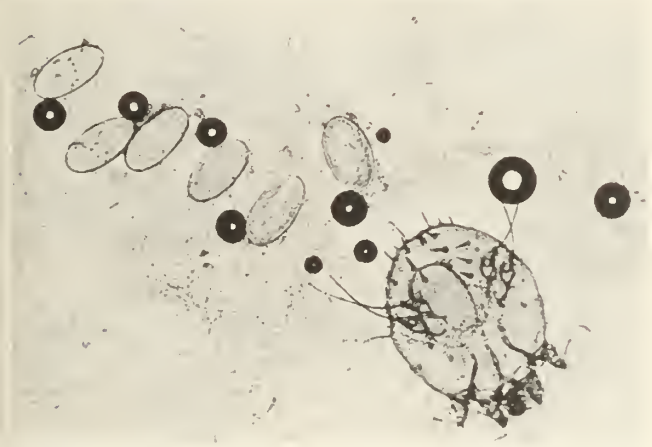

Figure 1.—Adult *Sarcoptes scabiei* (potassium hydroxide preparation).

Figure 2.—Scabies on the hand.

Figure 3.—Scabies on male genitalia.

Figure 4.—*Pediculus humanus capitis.*

the pruritus. Secondary infections require treatment with systemic antibiotics. Scabietic nodules may not respond to topical steroids. Here intralesional or even systemic steroids may be helpful.

Pediculosis (Lice)

Parasite

Pediculosis is skin infestation by a 2- to 3-mm wingless flat-bodied insect with three pairs of lateral legs ending in "claws" (Figures 4 and 5). Three different varieties of lice may infest humans: *Pediculus humanus corporis* (body louse), *Pediculus humanus capitis* (head louse) and *Phthirus pubis* (pubic crab louse). The fertilized adult lays her eggs either on body hairs or fibers of clothing. These eggs are referred to as nits. After seven to ten days, small nymphs emerge from the eggs and molt three times before becoming adults. The female produces as many as 250 eggs during her life span which lasts approximately 30 to 35 days. Adult lice attach themselves to the skin, living on the blood they suck. On piercing the skin, they release saliva which is antigenic and causes pruritus and subsequent dermatitis.

Figure 5.—*Phthirus pubis*.

Figure 6.—Pediculosis capitis.

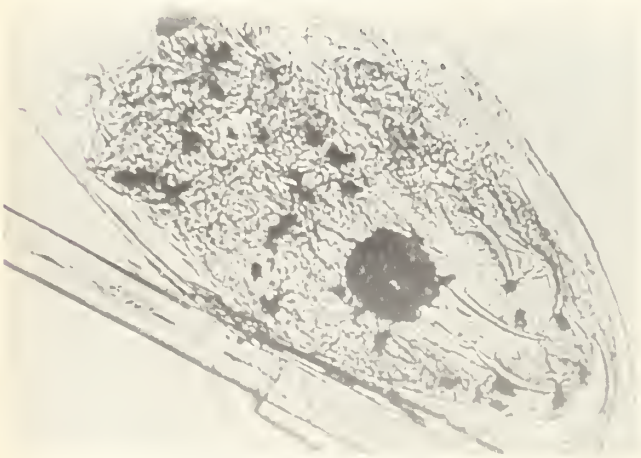

Figure 7.—Nit on hair.

Clinical Presentation

Infestation with *Pediculus humanis corporis* has also been called "vagabond's disease." It is most frequently seen in lower socioeconomic groups, associated with poor personal hygiene. The body louse lives mainly in seams of clothing and bedding. Very few are attached to human hairs and they are rarely found on the body during physical examination. The louse does descend to the skin for feeding. This subsequently causes generalized itching and papular or urticarial lesions. Secondary impetiginization may occur.

Pediculus humanus capitis can occur in all age groups, but is most frequently seen in younger school age children. This variety of louse usually limits itself to infestation of the scalp hairs, especially on the back of the neck (Figure 6). Pruritus is the major symptom leading to excoriation, secondary infection and lymphadenopathy. The pruritus and infection may be severe enough to cause irritability and restlessness. Diagnosis is made by identification of the parasite or the nit (Figure 7).

Phthirus pubis is most frequently found in adults and is contracted through sexual partners or infested clothing and bedding. The pubic crab louse usually limits itself to pubic hair extending from the umbilicus to the knees; however, it can migrate to the axillae and beard. Eyelash involvement is common in children who place their heads in the laps of infected adults. These lice can be difficult to find, but the nits usually can be seen attached to the hair shaft. Pruritus may be intense, although some persons are less bothered by the itching than by the sight of nits and lice. Occasionally, blue macules approximately 5 mm in diameter are seen on the lower abdomen and on the inner aspect of the thighs. These macules are called maculae caeruleae and are probably produced by alterated blood pigments at the site of the bites. As with pediculosis capitis, there may be excoriation with secondary infection and local lymphadenopathy. Extreme sensitivity to the bites may cause bullous lesions.

Treatment

The treatment for pediculosis is similar to that for scabies. For pediculosis pubis and pediculosis capitis, Kwell shampoo is extremely effective. The hair should

be thoroughly washed, rinsed, and the remaining nits combed out with a fine tooth comb. If a second application is needed, it should not be repeated for at least seven days. Crotamiton (Eurax), benzyl benzoate, malathion (Prioderm) and pyrethrin (Rid) can also be used. Pyrethrin is available without prescription. Sexual contacts of those with pediculosis pubis should also be treated. Eyelid involvement may be treated by the application of petrolatum twice a day for eight days, followed by the removal of any remaining nits.

Application of pediculicides for patients with body lice is usually not necessary. These patients need to wash or dry clean their clothes. Alternatively, the clothes can be placed in a plastic bag for seven to ten days, during which the lice will die. In body lice epidemics, DDT powder or benzene hexachloride (Lindane) can be dusted on clothing for the population at risk. As in scabies, secondary infection should be treated with systemic antibiotics. Eczematized areas may need topical or even systemic corticosteroids to clear the lesions.

Fleas

Parasite

Fleas are members of the insect order Siphonaptera, wingless 1- to 4-mm long blood-sucking ectoparasites of mammals and birds. Fleas take several blood meals a day, especially before laying eggs. A female flea lays her eggs on her host or in household crevices. Eggs hatch into larvae over a few days to weeks, depending on environmental conditions. Then larvae grow in cocoons to reach adulthood.

Clinical Presentation

Fleas are the vectors of plague and murine typhus. Flea bites most often occur on the legs and exposed areas of the body. These bites are usually erythematous and papular; in hypersensitive persons these lesions may become vesicular or even bullous. Flea bites are quite pruritic and secondary infection can become a problem. *Tunga penetrans* ("jigger flea," "chigoe") is commonly found in Latin America and Africa; this flea burrows below the stratum corneum of toes and fingernails and causes subcutaneous abscesses.

Treatment

Topical steroids and antihistamines are used to alleviate pruritus. Flea-infested rooms should be sprayed repeatedly to kill adult fleas emerging from cocoons. Flea-ridden domestic animals can be washed with insecticidal shampoo (malathion, for instance), dusted with DDT powder or fitted with a plastic "flea collar" impregnated with dichlorvos.

Ticks

Parasite

Ticks are eight-legged insects which are either soft bodied (Argasidae) or possess a hard, dorsal shell (Ixodidae). Argasidae live apart from the host in burrows or crevices, and emerge at night to bite and suck blood. The most common genus of soft ticks is *Ornithodoros,* vectors of relapsing fever *(Borrelia).* Ixodidae attach to the host during their complete life cycle (larvae, nymph, adult) and drop off the skin only when they become engorged with blood or die. There are 12 genera of hard ticks including *Dermacenter, Amblyomma, Ixodes* and *Rhipicephalus.*

Clinical Presentation

Usually the bite of a tick is painless, although occasionally a tick granuloma can occur. Hard ticks can cause tick paralysis, probably secondary to a neurotoxin in tick saliva. This paralysis may involve the pharynx, extremities, respiratory muscles and heart. Hard ticks can also transmit several diseases including viral encephalitis, tularemia, Rocky Mountain spotted fever, Q fever, Colorado tick fever, *Babesia* and erythema chronicum migrans (Lyme disease).

Treatment

Any patient with fever and possible tick exposure should be examined carefully for ticks and evidence of any of the previously mentioned transmissible diseases. Hard ticks can be removed by applying ether, acetone or benzene to the tick in order to loosen its mouth parts. Ticks also can be burned off or surgically excised. In regions with heavy infestation, protective clothing should be worn and areas such as the neck, scalp, wrists and ankles should be frequently inspected for ticks. Also tick repellents such as 30% N-butyl acetanilide can be used.

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Rabies Preexposure Prophylaxis

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One of a series of articles from western state public health departments

Rabies preexposure prophylaxis, protection for persons at "high risk" of future exposures to rabies virus, has generally received less attention than postexposure prophylaxis, the protection of persons after exposure to rabid or potentially rabid animals. Recent developments in rabies vaccine testing and technology for preexposure prophylaxis justify new interest from both public health and private practitioner viewpoints.

Preexposure prophylaxis with rabies vaccines became feasible and reasonable following development of rabies vaccines with a sufficiently low risk of serious side effects to warrant their preexposure use.[1] Preexposure prophylaxis has three potentially attractive features.[2] First, preexposure prophylaxis may protect the recipient against inapparent exposures to rabies virus—as could happen when the diagnosis of rabies is not considered in an animal biting a veterinarian or when an accident occurs in a laboratory handling live rabies virus. Second, if a victim's ability to obtain prompt postexposure prophylaxis is impaired, as might occur on an expedition in remote areas or to a missionary or health worker in third-world countries, preexposure prophylaxis may provide a level of protection against rabies while awaiting the start of postexposure prophylaxis. Third, since a preexposure prophylaxis recipient develops an anamnestic serologic response to subsequent rabies vaccine injections, the recipient's postexposure prophylactic regimen is cheaper and simpler than for those who have not received preexposure prophylaxis. Specifically, postexposure prophylaxis for preexposure prophylaxis recipients requires only two separate intramuscular injections of rabies vaccine three days apart, compared with the standard postexposure prophylactic course of five intramuscular vaccine injections over a 28-day period plus a single injection of rabies antiserum.[2] At current prices for human diploid cell vaccine (HDCV) and human rabies immune globulin (RIG) for a 70-kg person, the cost differential between these two postexposure regimens is approximately $335 (at a cost of $42.50 per HDVC dose, $160 for RIG and $15 per medical visit). Additional arguments favoring preexposure prophylaxis include the extreme rarity of rabies among preexposure prophylaxis recipients known to have responded serologically to rabies vaccine[3] and the safety of HDCV compared with all previously available rabies vaccines.[4] Reactions to HDCV are generally mild, with approximately 25% of recipients reporting local reactions and 20% experiencing systemic reactions such as headache, nausea or myalgia.[2] Allergic reactions are rare. Two cases of transient neuroparalytic illness among more than 330,000 HDCV recipients worldwide have been reported.[5]

The important new work in preexposure prophylaxis involves an intradermal regimen using HDCV.[6,7] As recently summarized by the Centers for Disease Control, all of more than 1,500 people lacking rabies antibody who received three 0.1 ml doses of HDCV intradermally (one dose each on days 0, 7 and 21 or 28) developed adequate antibody titers.[8] The intradermal injections are given in the skin overlying the deltoid to increase the probability of actual intradermal delivery; however, inadvertent subcutaneous administration also appears effective in inducing antibody production.[7] The high immunogenicity of HDCV virtually guarantees seroconversion in immunologically normal persons. Therefore, with the exception of persons known to be immunocompromised and workers in rabies vaccine production or rabies research, serologic testing to document a "take" of HDCV following preexposure prophylaxis is not recommended.[9] Finally, by the end of 1983 one of the two manufacturers of rabies vaccine licensed for use in the United States (Merieux Institute) plans to market HDCV in a special package for intradermal use only, at an estimated per dose cost of $15. Pending release of this package, currently avail-

Refer to: Mann J, Burkhart MJ: Rabies preexposure prophylaxis (Public Health and Preventive Medicine). West J Med 1983 Sep; 139:386-387.

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ABBREVIATIONS USED IN TEXT

HDCV = human diploid cell rabies vaccine
RIG = (human) rabies immune globulin

able 1-ml HDCV vials may be used for intradermal vaccine administration, but the vials are not intended for multidose use.

Candidates for preexposure prophylaxis include persons whose vocation, avocation or special circumstances place them at higher than average risk for exposure to rabies and particularly to risk of inapparent or unnoticed exposure to the virus. Veterinarians; veterinary assistants; animal control officers; trappers, spelunkers; biologists working with animal hosts of rabies virus (bats, skunks, raccoons, foxes and other species at high risk); laboratory workers in rabies diagnostic, veterinary, rabies vaccine and rabies research laboratories; travelers to certain rabies-enzootic areas (particularly where dog rabies is enzootic), and missionaries or health workers residing in rabies-enzootic areas can all be considered for preexposure prophylaxis.[1,2,7] While the proportion of candidates who actually receive preexposure prophylaxis is unknown, our experience in New Mexico suggests that few veterinary assistants, trappers or naturalists and only a minority of animal control workers have been vaccinated. In addition, while most veterinary students in the past five years have received preexposure prophylaxis in veterinary school, older veterinarians may lack adequate preexposure prophylaxis.

If preexposure prophylaxis is to be given, the recipient must understand that it cannot be relied upon for protection against rabies. Rather, if exposed to a rabid or potentially rabid animal, a limited postexposure prophylactic regimen (described above) will be necessary. Finally, if ongoing preexposure prophylaxis is desired, the Centers for Disease Control recommend that a single 0.1 ml intradermal booster dose of HDCV be administered every two years (exceptions are rabies vaccine and research workers who require closer monitoring and may need periodic titer checks and more frequent boosters).[2,8]

Now that preexposure prophylaxis is extremely safe and the vaccine cost will be greatly reduced, public health officials should consider strategies to increase preexposure prophylaxis coverage of selected high-risk groups. Physicians should welcome the advent of intradermal HDCV use, systematically question patients about their possible need for preexposure prophylaxis and consult with local and state health departments if questions arise regarding indications, details of administration and side effects of HDCV.

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Special Article

California's Approach to Hypertension Control: An Overview

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California's Department of Health Services, recognizing the serious community health problem presented by uncontrolled hypertension, developed community-based programs of early detection and referral, follow-up and education. Special consideration was given to underserved populations at high risk. A statewide probability household survey was conducted and showed an improvement in control status during the past decade for definite and critical hypertension, but not for mild hypertension. With diminishing public resources, future efforts must be cost effective, focus on care for persons known to have hypertension and encourage maximum coordination between private and public agencies.

It is estimated that more than 3 million adults have uncontrolled hypertension in California alone.[1] Approximately 66,000 deaths from heart disease and 17,000 deaths from stroke occur in the state each year.[2] By the early 1970s it had become clear that control of hypertension could prevent or postpone a significant proportion of these deaths.[3,4] In 1972 the National Heart, Lung, and Blood Institute undertook a nationwide educational program to promote awareness of the importance of early detection, treatment and control of high blood pressure among the public as well as health professionals. Similar programs were begun in California under the auspices of the California State Department of Health Services (formerly, the Department of Health), the California Heart Association, the California Medical Association and other agencies.

The purpose of this paper is to describe the program developed by the state's Department of Health Services and to present current data regarding hypertension prevalence and levels of awareness, treatment and control in the population of the state.

California's Program

The California Department of Health Services, in collaboration with a broadly based advisory group, actively participated in the development of a long-range plan for a coordinated approach to the problem of hypertension control. The work of the group was completed in 1976 with the adoption and publication of a two-volume document entitled *California State Plan for High Blood Pressure Control.*[5]

Four basic strategies were delineated in the state plan: increase consumer participation, improve the planning process, improve the distribution of high blood pressure services and improve the delivery of these services.

In November 1976 a state Hypertension Advisory Council was formed to make recommendations to the Director of the Department of Health Services concerning the implementation of the plan. In addition to the creation of its own Hypertension Control Program, the department has supported as many as 30 local hypertension control projects throughout the state. For all projects, activities were tailored to meet local community needs and utilize four basic program components to implement the strategies presented in the state plan.

Program Components

Screening and detection is the process of finding persons with elevated blood pressure who are unaware of their status. Screening may occur in a variety of sites including physicians' offices, outpatient clinics, health centers and various community screening sites. It is well recognized that screening in the absence of follow-up is of little value. California's program, therefore, requires that all screening activities have adequate pro-

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visions for referral to appropriate sources of care and follow-up.

Public education regarding hypertension revolves around two basic facts: High blood pressure is a serious health problem and high blood pressure can be treated. In addition, patient education stresses the importance of adherence to medical, dietary and other regimens. Local projects, especially those housed in community clinics, serve as a resource to the medical staff in providing this education.

Professional education, especially techniques of improving patient adherence to prescribed regimens, is of particular interest to the state program. Many of the local projects, in collaboration with university extensions, hospital staffs or professional societies, have sponsored seminars and developed programs on hypertension-related topics as part of their professional education efforts.

Coordination among physicians, clinics and other health agencies is an essential part of the program. Coordination requires agreement on referral criteria, willingness to accept referrals and sharing of information among responsible health professionals—especially as it relates to availability of services.

Local Program Activities

In order to fully address the problem hypertension presents in California, the Department of Health Services has sponsored local programs of three types: (1) service-oriented projects, (2) local hypertension coordinating councils and (3) ethnically oriented task forces. The ultimate goal of projects is to locate hypertensive persons, provide assistance in gaining access to a system of medical care and assure continuity and quality of care so that each person's blood pressure remains under control. Local councils work towards increasing the public's awareness of hypertension as a serious health problem and emphasize the importance of early diagnosis and long-term treatment of the disease. Because California's population of 24 million is culturally and ethnically heterogeneous, ethnically oriented task forces work with the state's minority groups. In addition, with the advice and concurrence of the Hypertension Advisory Council, priority is given to serving medically underserved populations, which often consist of ethnic minorities, such as blacks, known to be at high risk of developing hypertension.

In recent years, much has been written about community approaches to high blood pressure control. The following discussion presents three examples of interventions developed and supported by the Department of Health Services to address problems in hypertension control unique to California.

- *The East Bay Health Providers' Task Force,* a group of health professionals patterned after the National Black Health Providers' Task Force, has focused primarily on private providers and other health professionals serving the second largest black community in California (Alameda County). Thirty active task force members work through three committees (Physician's Advisory, Nutrition Advocacy and Supportive Services) to develop a model of community services aimed at increasing patient adherence to prescribed medical regimens.

In addition to reaching a consensus regarding use of common protocols for the care of hypertensive patients, the providers have developed professional education programs and implemented supportive services. This model of a working partnership between the private medical sector and community support systems, such as health education and nutrition counseling, is being adopted in other parts of the state.

- *The Venice Family Clinic* has established a weekly clinic which provides walk-in blood pressure screening, patient education, follow-up screening, diagnosis and treatment services (which the clinic itself pays for). Under the guidance of regular clinic staff, family practice residents from the University of California at Los Angeles complete month-long rotations at the clinic and are trained in stepped care hypertension management. Student volunteers planning careers in medicine and public health also assist in the clinic.

During the past year, the Venice clinic's program successfully reached its target population: 46% of those screened in the clinic were male, 69% were Hispanic and 53% were between the ages of 19 and 35. The detection rate has consistently been about 20%; in most of the cases the persons had been unaware of their elevated blood pressure. Of those who had been aware of their elevated blood pressure, most had never been treated.

The results of a study, conducted by a graduate student in public health at UCLA, indicated that in 53% of the Venice clinic's clients diagnosed as hypertensive there was either a 10 mm reduction in diastolic or systolic blood pressure, or blood pressure control was achieved (lower than 140/90 mm of mercury).

- In 1978 the Los Angeles High Blood Pressure Council, in conjunction with the National High Blood Pressure Education Program, state staff and over 300 Hispanic/Latino leaders, sponsored the first *California Conference on High Blood Pressure Among Spanish Speaking People.* Physicians and health professionals from both sides of the border explored clinical aspects, epidemiology, research and practical nutritional approaches relating to high blood pressure control among the state's Hispanic/Latino population. A second conference was held in February 1982 to assess progress and to continue to address the special needs of this group.

A similar conference was organized by the *Asian/Pacific Islander High Blood Pressure Task Force* in 1981. The 1979 California Hypertension Survey findings indicated high prevalence and poor control of high blood pressure among Asian and Pacific islanders, particularly the Filipino population. The major focus of the conference was to identify and address special problems, such as high sodium content diets, language barriers, cultural isolation and limited access to med-

ical care, which impede adequate control of hypertension.

Technical Assistance

In addition to sponsoring and monitoring 30 local projects similar to those presented above, state staff provide technical assistance to many other local and statewide organizations engaged in high blood pressure control activities. Program staff, with expert advice from a technical subcommittee of the Hypertension Advisory Council, have developed and widely distributed a protocol for screening, detection, diagnosis, treatment and follow-up of hypertensive persons.[6]

Effects of the Program

One way of assessing the effects of a statewide coordinated hypertension program is to examine trends of morbidity and mortality from heart disease, stroke and other hypertension-related diseases. In recent years, there has been a significant decrease in mortality from both myocardial infarction and cerebrovascular diseases.[7] The latter is probably attributable to better control of hypertension; the causes of the former require further study.[8]

Some assessment of program effects may also be achieved through two temporally separate measurements of prevalence, awareness and adequate treatment levels among California's population. In 1979 California conducted a statewide high blood pressure survey. Data from a second survey (1982-1983) are being analyzed and should provide direct assessment of the trends in the state during that interval. In addition, although not strictly analogous, information from the 1979 survey can be compared with earlier national data to gain some approximation of long-term trends.

In discussing the statewide survey, several specific issues will be addressed. First, what proportion of the California adult population falls into the following categories: (1) uncontrolled critical hypertension (diastolic blood pressure greater than or equal to 105), (2) uncontrolled definite or critical hypertension (diastolic greater than or equal to 95 or systolic blood pressure greater than or equal to 160) and (3) uncontrolled mild, definite or critical hypertension (diastolic greater than or equal to 90 or systolic blood pressure greater than or equal to 140 mm of mercury)? Further, how do these rates vary by race/ethnicity, by age and by sex?

Second, considering all persons who have hypertension, what proportion have blood pressure under control (by means of appropriate treatment)? What proportion have had their blood pressure measured recently? What proportion are aware of their condition and what proportion are under appropriate treatment?

Third, to what extent do the findings of the survey indicate progress compared with earlier studies, and where should future public health efforts be directed to make further progress?

TABLE 1.—*Sample Size, Population Estimate and Percent Born in the United States*
(CALIFORNIA 1979)

	Sample Size		*Population Estimate**		*Percent of Sample Born in US*
	N	%	*N(000s)*	%	
OVERALL	8,353	100.0	15,852	100.0	71.6
Age					
18-49 years	5,724	68.5	10,408	65.7	71.9
50+ years	2,629	31.5	5,437	34.3	71.0
Sex					
Male	3,898	46.7	7,639	48.2	70.8
Female	4,455	53.3	8,213	51.8	72.3
Race/Ethnicity					
White and other	3,396	40.6	11,492	72.5	91.5
Black	1,436	17.2	1,133	7.1	98.5
Asian/Pacific Islander	1,757	21.0	792	5.0	32.0
Hispanic	1,764	21.1	2,433	15.4	50.4
Asian/Pacific Islander Subgroups					
Chinese	644	7.7	267	1.7	21.7
Japanese	453	5.4	172	1.1	73.6
Filipino	422	5.1	219	1.4	13.6
Other Asian	238	2.8	132	.8	11.8
Education					
Eighth grade or less	1,341	16.1	1,564	10.2	33.5
Some high school	1,153	13.8	2,083	13.3	75.7
High school graduate	2,440	29.2	4,777	30.6	78.6
Some college	2,076	24.9	4,268	27.3	80.1
College graduate	876	10.5	1,860	11.9	70.0
Postgraduate	454	5.4	1,026	6.6	75.1

Source: 1979 California Hypertension Survey. Civilian noninstitutionalized population aged 18 and over.

* Population estimates for totals and subgroups are based on sample projections; the subgroup estimates do not always add up to the given totals because of loss of precision due to rounding off or to missing data.

Methods

Detailed descriptions of the methods of the 1979 California hypertension survey are presented elsewhere.[1,9,10]

Briefly, using standard probability sampling techniques, in 1979 a representative sample of California's civilian, noninstitutionalized population, consisting of 8,353 persons 18 years old or older (residing in 4,367 randomly selected households) was interviewed and their blood pressure was measured. The interview covered a wide range of public health issues, primarily focused on risk factors associated with heart disease (obesity, diet, exercise, other aspects of life-style), as well as knowledge and awareness of hypertension.

Of the households selected, 85% provided enough information to determine the number of adults residing at the selected addresses. Of the adults so enumerated, 85% responded to the questionnaire and had their blood pressure measured. Interviewers recorded three blood pressure readings for each respondent. The average of the second and third readings was used for the analysis presented here.

Table 1 presents basic demographic information on the sample. While prevalence of hypertension among blacks is well documented, its prevalence among Asian/Pacific islanders is less known. Thus, part of the plan was to oversample two of California's major population groups: (1) blacks and (2) Asians and Pacific islanders. Sufficiently large numbers of the two groups were included to allow for meaningful statewide estimates of the prevalence of hypertension among them. Using appropriate statistical techniques, the findings in the sample were used to make projections concerning the entire adult, noninstitutionalized population of California as of 1979. The methodology included an adjustment for nonresponse.

Findings

Prevalence

On the basis of previous information,[11] it was expected that roughly 5% of the adult population would have a diastolic blood pressure of 105 mm of mercury and above. However, a much lower estimate (1%) was obtained from the 1979 survey (Table 2). Even this low prevalence is extremely important because it means an estimated 153,000 Californians have uncontrolled critical hypertension.

Until recently hypertension was considered "definitely present" only when blood pressure levels were consistently higher than 160/95 mm of mercury. Using

TABLE 2.—*Prevalence of Uncontrolled Hypertension*
(CALIFORNIA 1979)

	Uncontrolled Critical: DBP 105+		*Uncontrolled Definite and Critical: 160/95+*		*Uncontrolled Mild, Definite and Critical: 140/90+*	
	*N(000s)**	*%*	*N(000s)**	*%*	*N(000s)**	*%*
OVERALL	153	1.0	1,046	6.6	3,139	19.8
Age						
18-49 years	52	0.5	343	3.3	1,114	10.7
50+ years	98	1.8	701	12.9	2,033	37.4
Sex						
Male	99	1.3	596	7.8	1,795	23.5
Female	49	0.6	452	5.5	1,355	16.5
Race/Ethnicity						
White and other	101	0.9	727	6.6	2,344	20.4
Black	23	2.0	116	10.2	296	26.1
Asian/Pacific Islander	8	1.0	55	7.0	143	18.1
Hispanic	20	0.8	114	4.7	384	15.8
Asian/Pacific Islander Subgroups†						
Chinese	1	0.2	15	5.8	42	15.7
Japanese	1	0.2	7	4.3	22	12.5
Filipino	4	2.0	22	9.9	32	24.5
Education						
Eighth grade or less	19	1.2	166	10.3	477	30.5
Some high school	31	1.5	212	10.0	533	25.6
High school graduate	30	.6	274	5.6	879	18.4
Some college	37	.9	241	5.6	700	16.4
College graduate	26	1.4	74	3.9	335	18.0
Postgraduate	9	.9	81	7.8	166	16.2
US (1971-74)‡		4.9		18.4		36.0
US (1974-75)‡		3.8		16.9		33.0

DBP = diastolic blood pressure
Source: 1979 California Hypertension Survey. Civilian noninstitutionalized population aged 18 and over.

* Population estimates for totals and subgroups are based on sample projections; the subgroup estimates do not always add up to the given totals because of loss of precision due to rounding off or to missing data.
† "Other Asian" excluded, not enough cases for reliable estimates.
‡ Source: Tables 48, 49, 50 in reference 12. Note: Figures are based on the average of three blood pressure measurements for adults aged 25-74.

TABLE 3.—*Screening for High Blood Pressure*
(CALIFORNIA 1979)

	% Blood Pressure Taken Within the Last 2 Years	*Physician in the Last Year*
OVERALL	88.4	78.3
Age		
18-49 years	87.0	76.6
50+ years	91.1	81.5
Sex		
Male	85.4	71.8
Female	91.2	84.3
Race/Ethnicity		
White and other	89.4	79.9
Black	91.7	82.9
Asian/Pacific Islander	81.9	69.3
Hispanic	84.0	71.5
Asian/Pacific Islander Subgroups		
Chinese	82.6	67.4
Japanese	81.1	73.4
Filipino	83.5	69.5
Other Asian	78.7	67.8
Education		
Eighth grade or less	81.6	70.8
Some high school	87.2	78.5
High school graduate	88.4	78.7
Some college	90.6	81.5
College graduate	86.7	76.2
Postgraduate	94.5	77.8

Source: 1979 California Hypertension Survey. Civilian noninstitutionalized population aged 18 and over.

this criterion, the survey obtained the following estimated rates (Table 2): overall, 6.6%; whites, 6.6%; blacks, 10.2%; Asian/Pacific islanders, 7.0%; and Hispanics, 4.7%. These rates are much lower than the 17% to 18% rate reported by previous national studies.[12]

With the inclusion of uncontrolled mild hypertension (blood pressure of 140/90 mm of mercury or above), the total prevalence becomes 19.8% (Table 2). This is much lower than the overall rate reported for the United States in 1971-1974 (36.0%) and in 1974-1975 (33.0%).[12] The cutoff point of 140 or higher systolic or 90 mm of mercury or higher diastolic is important in light of the findings of the Hypertension Detection and Follow-up Program indicating that treatment of mild hypertension is of value.[13]

It should be noted that estimates of prevalence vary between men and women (23.5% versus 16.5%). Analysis of prevalence by ethnicity indicates that blacks have an elevated blood pressure about 33% higher than whites (26.1% versus 20.4%). Hispanics and Asian/Pacific islanders, as a group, have somewhat lower prevalence rates (15.8% and 18.1%). Among the different Asian/Pacific islander subgroups, however, Filipinos have the highest prevalence (24.5%), second only to blacks.

Awareness, Treatment and Control

A great deal of effort has been devoted in recent years to focusing attention on the importance of periodic blood pressure measurements. As estimated by the 1979 survey, fully 80% of California's population had their blood pressure measured "in the past year," and 88% did so "in the past two years." These figures hold true for all major population groups (Table 3).

Table 4 presents data on the awareness, treatment and control status of those with hypertension. "Awareness" is defined by an answer of "yes" to the following question: "Have you ever been told by a doctor that you had high blood pressure?" "Under treatment" is defined by an answer of "yes" to the question, "Are you now taking medicine for high blood pressure?" "Controlled" is defined as a blood pressure reading (average of second and third) less than 140/90 mm of mercury.

In this context hypertension is further defined, not only in terms of blood pressure, but also in terms of treatment status. Hypertension, as recorded in Table 4, is defined as a systolic blood pressure of 140 or higher or a diastolic blood pressure of 90 mm of mercury or higher. It *also* includes those persons who stated that they were currently taking medicine for high blood pressure, regardless of their current blood pressure levels. The distribution of figures in this table for people with hypertension corresponds generally to the pattern already described for uncontrolled hypertension.

Overall, 59% of those with hypertension are aware of their condition, 40% are aware *and* under treatment (taking medication) and 16% are aware, under treatment and controlled (blood pressure lower than 140/90 mm of mercury). The data clearly show men to be in a less favorable situation than women. As might be expected, the level of awareness, treatment and control of hypertension generally increases with age, though an upper threshold appears to be in effect by the middle of the fifth decade. Rather surprisingly, analysis of awareness, treatment and control by educational level does not show those with the least amount of formal education to be at greatest risk despite their high prevalence rates. A similar trend is observed for income levels.

The data on awareness, treatment status and control of hypertension by ethnicity show that among all Californians, blacks have the highest level of awareness, treatment and control, while Hispanics and Asian/Pacific islanders exhibit a relatively low awareness, treatment and control status. Among the Asian/Pacific islanders, Filipinos exhibit a high level of awareness and treatment, but their hypertension is very poorly controlled. In fact, only about one of six Filipinos who state that they are taking medication for hypertension has normal readings as compared with one of two or three in all other groups.

Implications for Future Activities

Results of the 1979 California surveys should be analyzed to plan for the best use of limited available tax money to achieve the goal of maximum control of high blood pressure in California. While expenditures for the state's Hypertension Control Program were $1.7 million during FY 1982-1983, Medicaid (Medi-Cal) claims for hospital admissions for heart disease

and stroke *alone* reached nearly $32 million in 1979. Thorough review and analysis of these fiscal and epidemiologic data by staff and the Hypertension Advisory Council have led the Department of Health Services to adopt the following program priorities:

1. Those people whose blood pressure is elevated, but who are not currently receiving care, should be brought into the health care system. Approximately 2 million Californians are in this group.

2. Those hypertensive persons who are currently in the health care system, but who still have elevated blood pressure, should be encouraged to achieve the normotensive state. Approximately 1.1 million Californians are in this group.

3. The current screening level, approximately 80% per year, should be maintained, but the referral and follow-up mechanisms should be strengthened.

As to population subgroups, public programs will continue to focus on the medically underserved and on ethnic groups at high risk. They will also give special attention to men under the age of 50 years because of the latter's low awareness, treatment and control rates. Work-site programs may be an effective way of reaching this group.

The fact that more than 1 million people in California are receiving antihypertension medication but still have elevated blood pressure suggests either noncompliance by patients, inadequate treatment or both. This emphasizes the need for more effective patient, family and professional education. Efficient physician counseling of patients is clearly indispensable.

Recent findings from the Multiple Risk Factor Intervention Trial have raised questions about pharmacologic treatment of patients with mild hypertension.[14] The Department of Health Services has responded by advising its hypertension control projects that the following should be done until this problem is reviewed by the Advisory Council's technical advisors or additional clarifying data become available from the National Heart, Lung, and Blood Institute or others: (1) all persons with elevated blood pressure should be counseled regarding nonpharmacologic approaches especially related to salt restriction, weight control and supervised

TABLE 4.—*Prevalence and Hypertension Status by Selected Demographic Characteristics*
(CALIFORNIA 1979)

Demographic Characteristic	*Population Estimate N(000s)**	*% Hypertensive*	*% Hypertensive Subjects Who Are:*		
			Aware†	*Under Treatment‡*	*Controlled§*
OVERALL	15,852	24.0	59.5	39.7	16.2
Age (in years)					
18-29	4,812	7.7	30.7	8.2	4.1
30-39	3,300	11.6	47.2	21.7	12.3
40-49	2,302	22.0	56.5	33.5	16.5
50-59	2,382	36.1	66.7	44.1	16.9
60-69	1,750	49.7	65.5	47.2	22.2
70+	1,309	62.2	66.2	53.6	16.3
Sex					
Male	7,638	26.6	52.1	29.9	11.1
Female	8,212	21.6	68.0	51.0	22.1
Race/Ethnicity					
White and other	11,492	24.4	60.2	39.8	16.7
Black	1,133	33.8	64.7	49.2	20.7
Asian/Pacific Islander	792	20.0	54.2	36.0	8.7
Hispanic	2,433	18.6	52.4	31.9	11.9
Asian/Pacific Islander Subgroups					
Chinese	267	18.1	45.6	35.3	13.0
Japanese	172	14.1	55.6	27.4	8.2
Filipino	219	26.6	63.4	49.0	7.9
Education					
Eighth grade or less	1,610	37.9	57.0	43.3	16.4
Some high school	2,115	30.5	60.2	40.5	15.7
High school graduate	4,850	22.8	59.1	41.9	18.2
Some college	4,327	19.3	62.6	39.5	14.3
College graduate	1,885	20.1	57.5	30.3	10.4
Postgraduate	1,048	21.5	59.4	34.2	24.6
UC (1971-74)‖		38.1	42.0	24.4	5.5
US (1974-75)‖		35.8	51.9	27.2	7.8

Source: 1979 California Hypertension Survey. Civilian noninstitutionalized population aged 18 and over.

* Population estimates for totals and subgroups are based on sample projections; the subgroup estimates do not always add up to the given totals because of loss of precision due to rounding off or to missing data.
† Aware of high blood pressure.
‡ Aware and under treatment.
§ Aware, under treatment and controlled.
‖ Source: Tables 35, 36, 48, 50 in reference 12. Figures are based on the average of three blood pressure measurements for adults aged 25-74.

aerobic exercise and (2) decisions regarding pharmacologic treatment should be made by clinicians on an individual basis, considering age, race, sex, family history, target organ damage, relevant electrocardiographic findings and laboratory test results.

There is an imperative need for continuing professional education at all levels dealing with diverse but essential topics such as the stepped care approach in treatment, the pharmacology of newly available antihypertensive drugs, effective techniques in patient communication and means of giving emotional support to patients and their families.

A continuing effort to coordinate existing resources and services, both public and private, is required to achieve economy and efficiency, and build good hypertension control into rural health, family planning, county health and other public state and local programs. Community councils are working in a similar way with their local organizations, including medical societies, hospitals, clinics and voluntary health agencies.

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Medical Schools of the West

University of Arizona, College of Medicine

LOUIS J. KETTEL, MD, *Tucson, Arizona*

Springtime 1983 marked the 13th convocation ceremony for the College of Medicine at the University of Arizona. With this graduation 942 graduates (including 206 women) have entered the health care scene as physicians educated by the College. The experiences of the University of Arizona, the state of Arizona and all others involved that have led to this accomplishment have been described in previous writings. A fine case study written by Merlin K. DuVal, MD, the founding dean, is worthy of review.[1] An update of this report was prepared in 1981.[2]

A telescopic chronology of the events and highlights of the early history as described by Dean DuVal in 1981 follows:

- *1959.* A Commonwealth Fund grant to the Arizona Board of Regents in the amount of $135,000 put in place a team of consultants to study the need for a medical school in Arizona.
- *1962.* The Arizona Medical School Study (known familiarly as the Volker Report after the head of the consultant team, Joseph F. Volker, DDS, PhD, then Director of Research and Graduate Studies at the University of Alabama Medical Center) and its conclusions were endorsed by the Board of Regents.

In brief, the study concluded that Arizona would be well served by the establishment of a medical school and that resources were adequate to support a four-year school. The study further recommended building the school on the academic campus with the greatest level of graduate education development and that a teaching hospital of 300 or more beds be owned and operated by the school.

- *1963.* The legislature appropriated funds for the President of the University of Arizona to proceed with planning.
- *1964.* Dr Merlin K. DuVal, formerly professor of surgery and assistant director of the University of Oklahoma Medical Center, came to Arizona as the founding dean.
- *1964.* The state appropriation of $160,000 was added to a second Commonwealth Fund grant of $240,000 for planning to be used through fiscal year 1965.
- *1965.* The statewide fund raising by Founders for Arizona Medical Education (FAME), led by the late William R. Matthews, editor and publisher of the Tucson *Arizona Daily Star,* raised $3 million. Federal matching funds of $4.3 million were received to build the Basic Sciences Building.
- *1966.* The planning team was recruited. Oscar A. Thorup, Jr, MD, later to develop the Department of Internal Medicine, joined Dr DuVal to design the Clinical Sciences Building and teaching hospital. Philip H. Krutzsch, PhD, who later became professor and head of the Department of Anatomy, oversaw the design of the Basic Sciences Building. John D. Palmer, MD, PhD, developed the Multidiscipline Laboratories and David Bishop was responsible for creating the medical library.
- *1967.* November 17, 1967, was the dedication date for the Basic Sciences Building (Figure 1). The first of 32 medical students began studies in September 1967, almost precisely at the time the building was completed.
- *1971.* In May the first class graduated and held its convocation as the first official function in the Clinical Sciences Building (Figure 2). University Hospital admitted its first patients in September. Its construction was funded by the sale of $8.5 million in revenue bonds to be retired from student registration fees, and $14.8 million in matching funds from the Bureau of Health Manpower of the US Public Health Service.

Curriculum

During the planning period, discussions were held among the related academic disciplines at the University of Arizona. The possibility of a medical school built without its own basic science departments and dependent upon a relationship with the undergraduate

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campus was explored. Among the members of the potential disciplines, only those in microbiology expressed any interest in a tight relationship or shared resources. Those in other disciplines suggested the College of Medicine develop departments of its own. Hence the College of Medicine initially had independent departments of anatomy, biochemistry, microbiology, pharmacology and physiology. A four-year curriculum was designed traditionally with basic sciences taught in the first two years and clinical sciences and electives in the second two years. Recruiting followed along this decision, although innovative courses and approaches to education were a part of the curriculum from the start and so continue. An important and now timely decision was the establishment of a Division of Social Perspectives in Medicine to assure that topics such as ethics, health policy and socioeconomics were brought to the attention of faculty and students.

Figure 1.—The brick structure is the Multidiscipline Laboratories attached to and directly in front of the preformed concrete Basic Sciences Building behind.

From the first days, students were brought into contact with patients, virtually on entry to the College. This practice continues. The curricular philosophy emphasizes medical education as a continuum proceeding from the undergraduate years into graduate and postgraduate practice life. The curriculum goal is to educate physicians who will become lifelong learners of medicine. A major curricular innovation produced a three-year program begun in 1972. This experiment in education functionally telescoped the basic science teaching into approximately 18 calendar months and placed clinical topics in the remaining 18 months. As a part of this curricular revision, further innovative changes in curriculum and educational philosophy resulted in the development of a course in Human Behavior and Development and a modified approach to the introductory material in clinical medicine under the general rubric of Preparation for Clinical Medicine (see Figure 3). As a benefit of the three-year curriculum, it became possible to enlarge class size. By 1974 the entering class had increased from the initial 32 to the present class size of 88 entering students each year.

Because of the unique nature of a beginning medical school, a longitudinal study of graduates and their per-

Figure 2.—The main entrance to the Arizona Health Sciences Center is situated between University Hospital, the structure at the far right, and the Clinical Sciences Building containing research laboratories and patient examination physician offices.

Figure 3.—Paula Stillman, MD, is shown meeting with a freshman class during a Preparation for Clinical Medicine presentation. Physical examination of infants is demonstrated periodically during the year in a Multidiscipline Laboratories classroom.

formance has been maintained. With curricular innovations and a variety of different approaches to teaching established subjects, it has been important to monitor the performance of graduates. Arizona graduates perform well as measured by National Board of Medical Examiners testing and after graduation reflected in performance well above the national median on specialty board testing. Graduates are regularly licensed by the states in which they choose to practice. The attrition rate has remained less than 2% for all years of medical school and feedback from residency program directors indicates our graduates are among the best seen. Hence, neither the peculiarities characteristic of early curriculum development nor the innovation of a three-year curriculum have had a negative impact on performance.

For a number of reasons, perhaps the most important being the stresses caused by the pace of learning, the College returned to the traditional four-year curriculum in 1978. The innovative courses of the three-year curriculum were retained while released time during the summers was returned and a significantly slower pace of learning encouraged. Particularly important in this transition was a restructuring of the Preparation for Clinical Medicine course. Under the guidance of Paula L. Stillman, MD, Patient Instructors are used to teach interviewing and basic physical examination skills. This nationally recognized educational methodology has now been applied in the residency training programs and continuing medical education courses.

Selection Process

A college of medicine is known by its product, the physicians who have graduated from the school. From the first, the College admissions policy has sought applicants from a broad spectrum of backgrounds. Just as the curriculum evolved to assure that graduates could enter any discipline for further education, so the admissions process has developed to select students with a diversity of career goals. From the outset, the legislature intended that priority be given to residents of Arizona. Additionally, some applicants are admitted from states without medical schools and are eligible for Western Interstate Commission for Higher Education support. No special consideration has ever been given to any particular premedical school or major, but the College requires satisfactory accomplishment of studies in general and organic chemistry, physics, general biology or zoology, and English.

The selection of students depends on an evaluation of the premedical grade-point average, performance on the New Medical College Admission Test, a personal statement of interests, letters of recommendation, especially from premedical advisors, and the results of interviews by both the faculty and practicing physicians. At present 88 students enter each August.

The size of the graduating classes directly parallels the entering class. Because some students have chosen to take longer than the required curricular time to complete their course work, the number of graduates varies. The early classes of 1971 and 1972 were the smallest. The largest class was in 1975 when the change to the three-year curriculum caused an overlap with the four-year curriculum class and a total of 108 students graduated.

The graduating class in 1980 was unique. As a result of the curriculum expanding to four years in 1978, space was available in the third curriculum year. Thus the class comprised students who either extended their medical schooling to four years from the previous three-year curriculum or transferred into the College of Medicine at the beginning of the junior year. This graduating class was quite diverse, having both students educated completely in Arizona's College and students who received portions of their medical school education at medical schools in other states or countries.

Outcomes

While members of classes as early as 1976 remain in graduate training programs, it is now possible to look at practice and location trends of graduates. Of our graduates, 40% completed residency training in California and 36% in Arizona. Since most graduates practice close to their training programs, it is not surprising that a rather constant percentage of College of Medicine graduates begin practice in the state of Arizona. This has averaged 38% for the 11 graduating classes.

Because many graduates are still in training programs, it is difficult to make projections on future practice site selection or trends in final specialty choice. We do know that more than 54% of the graduates have been entering primary care specialty training programs in family practice, general internal medicine or general pediatrics. In 1981 our first decade's graduates were surveyed.[3] Two thirds of the respondents were already in practice, 55% in primary care and 63% board certified. Some 37% practice in cities with populations greater than 500,000, an additional 40% in moderate-sized cities and only 4% in rural areas. Of the practitioners, 33% continue to reside in Arizona. In Arizona

the selection of rural practice sites has included Safford, Yuma, Flagstaff, Miami, Globe, Morenci, Casa Grande, Prescott, Bisbee, Pinetop, Sierra Vista, various Indian Health Service reservation sites and the smaller communities surrounding Phoenix and Tucson. Our graduates were satisfied with their professional and personal life as determined by self-rankings. They also were quite satisfied with the training received from the University of Arizona College of Medicine.

Graduate Medical Education

Starting with the establishment of the internal medicine program in 1968, the clinical departments of the College quickly developed broad spectrum residency programs. These graduate programs now include anesthesiology, internal medicine and its specialties, surgery and its specialties, neurology, obstetrics and gynecology, ophthalmology, pediatrics, psychiatry, radiology and its specialties, preventive medicine, emergency medicine and family practice. More than 300 house officers and fellows are continuously in these College programs.

The Generation of New Knowledge

While the charge to the College was surely that of developing a strong educational program, implicit was the desire to provide a resource of new knowledge for Arizona. This, too, has developed superbly. Among the earliest accomplishments was the development of a perinatal and high-risk pregnancy transport service for the state. Working closely with the nucleus of such a program begun by Belton Meyers, MD, in the Phoenix area, the faculties of the Departments of Obstetrics and Gynecology and Pediatrics have developed a successful program which has brought national and indeed international regard and acclaim for Arizona. During the period of existence of the medical school, the infant mortality rate in Arizona has fallen dramatically.

Cancer research was early identified as a significant need. With clinical trials being the keystone of our direction, renown in oncologic therapy, both chemical and radiation, has evolved first under the leadership of Max Boone, MD, PhD, and continues under the current director, Sydney Salmon, MD, and his colleagues. There is national recognition of the importance of stem cell assays for therapeutic selection. The burgeoning of the cancer program has resulted in a plan for the first major building expansion in the form of a freestanding cancer center. Private fund raising is virtually complete and construction anticipated, with occupancy by 1985.

For years the state of Arizona has been a major center of care for those with respiratory illness. From the early days of tuberculosis therapy to the more modern treatment of asthma and obstructive lung diseases, thousands of patients come to the desert areas each year. The College has developed a major commitment to respiratory illnesses, their diagnosis and treatment, and research into causes. A longitudinal study of the natural history of respiratory illnesses in Pima County is in its tenth year under the leadership of Benjamin Burrows, MD. This program is a model of epidemiologic research and has prompted important new understandings of the natural history of obstructive respiratory illnesses. In response to enthusiasm for this program, a special addition to the Health Sciences Center was constructed in 1974 housing the Respiratory Science Division and the Specialized Center of Research which conducts these programs.

During these years of growth, programs valuable to the state have evolved in community psychiatry, multiple sclerosis research, investigations of muscular dystrophy and related disorders, diabetes, care of chronic renal illnesses, digitalis metabolism, drug pharmacology in aging, the care of chronically arthritic patients, anesthetic toxicology, cardiac and other organ transplants, surgical approaches to morbid obesity, joint replacement, blood vessel physiology, pineal gland research, neuropharmacology, the physiology and biochemistry of aging, geriatric care, occupational and environmental medicine, radiation therapy (particularly associated with hyperthermia), diagnostic imaging and plasmapheresis. To support these programs, centers devoted to respiratory illnesses, arthritis, occupational safety and health, long-term geriatric care, hemophilia, cancer, poison control, and postoperative prostheses and restorative medicine have evolved.

In its evolution, the College has developed a strong relationship with University Hospital. This institution, the laboratory of the College of Medicine for teaching and investigation, also functions as a superb community hospital with the best possible patient care its highest priority. The model of high quality patient care is the most important criterion for such a teaching institution. To that end, University Hospital is neither uniquely competitive, nor merely additive to other hospitals in the community. It does attempt to be a model in all areas of its work, but remains only one of the many affiliated institutions in the state that are necessary to provide all aspects of education for the College's programs.

The teaching base of patients could not be maintained if it were not for additional affiliations. Early in its development, the College depended heavily upon Veterans Administration and other governmental and community resources. The Tucson VA Medical Center has been critical in providing adult medicine and surgery opportunities in most clinical programs and has been the site of many innovative and productive research programs. These include projects in basic research on liver and alcohol, developmental applied research on amputation and prosthesis and delivery of health care using protocols and nonphysician providers.

The Kino Community Hospital of Pima County has been the center for pediatric ambulatory education and much of the obstetrics and gynecologic teaching. The Arizona-based Indian Health Service facilities have been important in primary care and community health education and research programs, especially in diabetes and tuberculosis.

Many community hospitals, as well as governmental hospitals in the Phoenix area, have provided a loosely

structured remote site clinical campus. Almost a third of the junior class takes required clerkships in internal medicine, pediatrics, neurology, obstetrics and gynecology and family practice in the Phoenix area. Many clinical electives that attract senior students are also provided in Phoenix. A number of the sites have become involved in basic and clinical research, perhaps best shown by graduate student assignment to research faculty at the Barrow Neurologic Institute affiliated with the Phoenix-based St Joseph's Hospital.

As an early outreach for community educators, the El Rio Santa Cruz Neighborhood Health Center was established. The Department of Family and Community Medicine activities originally spearheaded this program which now is community operated and includes its own health maintenance organization (HMO). The program continues as an important primary care model and teaching unit.

The Present and Future

The future of the College of Medicine is bright indeed. The faculty see their mission as achieving excellence in education, research and service. They include among their responsibilities graduate and continuing medical education especially for the physicians of Arizona. Research is focused in areas that are conceived as most needed in Arizona. Particularly noteworthy are the studies relating to cancer, respiratory disease, heart disease and arthritis. The service role centers on perinatal and high-risk pregnancy care, occupational medicine, cancer chemotherapy and radiation therapy, organ transplant and a variety of special procedures not generally available elsewhere in Arizona.

The earliest charge by the Board of Regents to the University of Arizona was to develop a College of Medicine of excellence. Second, the College was charged to build a unique teaching hospital. These ends have both been met. Arizona's College of Medicine and the Arizona Health Sciences Center are alive and well. We look to the decades ahead with pride and anticipation.

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In Memoriam

California Medical Association

ALLEY, RUSSELL L., Colusa. Died March 7, 1983, in Colusa, aged 71. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. MD degree from California College of Medicine, 1962. Dr Alley was a retired member of the Yuba-Sutter-Colusa Medical Society.

BARNETT, CHARLES W., Palo Alto. Died June 5, 1983, at Stanford University Hospital, aged 79. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1927. Dr. Barnett was a retired member of the Santa Clara County Medical Society.

BASSETT, J. BRANDON, Oakland. Died February 22, 1983, in Piedmont of myocardial infarct, aged 64. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1944. Dr Bassett was a member of the Alameda-Contra Costa Medical Association.

BODNER, HENRY, Los Angeles. Died March 17, 1983, aged 72. Graduate of Indiana University School of Medicine, Indianapolis, 1934. Licensed in California in 1937. Dr Bodner was a member of the Los Angeles County Medical Association.

BURTNESS, HILDAHL I., Santa Barbara. Died May 9, 1983, in Santa Barbara, aged 80. Graduate of Rush Medical College, Chicago, 1930. Licensed in California in 1930. Dr Burtness was a member of the Medical Society of Santa Barbara County.

CAHN, RONALD L., Los Gatos. Died March 19, 1983, in San Jose, aged 39. Graduate of Indiana University School of Medicine, Indianapolis, 1969. Licensed in Califonia in 1973. Dr Cahn was a member of the Santa Clara County Medical Society.

CAMPION, RICHARD S., Paradise. Died May 3, 1983, in Paradise of heart disease, aged 59. Graduate of the University of Minnesota Medical School, Minneapolis, 1950. Licensed in California in 1953. Dr Campion was a member of the Butte-Glenn Medical Society.

CORNELL, CHESTER E., South Laguna. Died February 20, 1983, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr Cornell was a retired member of the Los Angeles County Medical Association.

GRAESER, JAMES B., Oakland. Died June 18, 1983, in Oakland of cancer, aged 82. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1934. Dr Graeser was a retired member of the Alameda-Contra Costa Medical Association.

GWARTNEY, RICHARD H., San Bernardino. Died March 16, 1983, in San Bernardino of heart disease, aged 65. Graduate of the University of Southern California School of Medicine, Los Angeles, 1944. Licensed in California in 1944. Dr Gwartney was a member of the San Bernardino County Medical Society.

HOOK, WALTER ELISHA, San Francisco. Died February 21, 1983, in Oakland, aged 74. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1945. Dr Hook was a member of the San Francisco Medical Society.

JAARSMA, RAYMOND A., Riverside. Died May 28, 1983, in Flint, Michigan, aged 62. Graduate of Marquette University School of Medicine, Milwaukee, 1946. Licensed in California in 1964. Dr Jaarsma was a member of the Riverside County Medical Association.

JEW, JACK, San Francisco. Died May 21, 1983, in Switzerland, aged 56. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1954. Licensed in California in 1955. Dr Jew was a member of the San Francisco Medical Society.

KLOR, SAMUEL J., Modesto. Died January 13, 1983, in Riverside of heart disease, aged 71. Graduate of Indiana University School of Medicine, Indianapolis, 1936. Licensed in California in 1940. Dr Klor was a retired member of the Stanislaus Medical Society.

LEISKE, SAMUEL W., Lodi. Died February 17, 1983, in Lodi, aged 84. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Dr Leiske was a retired member of the San Joaquin County Medical Society.

LEMON, ELOISE M., San Clemente. Died May 31, 1983, of ruptured thoracic aortic aneurysm, aged 79. Graduate of Woman's Medical College of Pennsylvania, Philadelphia, 1949. Licensed in California in 1966. Dr Lemon was a member of the Orange County Medical Association.

LLOYD, CLARENCE LEE, Inglewood. Died December 24, 1982, aged 83. Graduate of Loyola University School of Medicine, Chicago, 1937. Licensed in California in 1941. Dr Lloyd was a member of the Los Angeles County Medical Association.

LONGWORTH, EDMUND F., Orange. Died October 3, 1982, of carcinoma of the pancreas, aged 69. Graduate of New York Medical College, 1937. Licensed in California in 1947. Dr Longworth was a retired member of the Orange County Medical Association.

MUNDY, CARROLL FRANCIS, Bakersfield. Died February 23, 1983, in Los Angeles of myocardial infarct, aged 64. Graduate of Washington University School of Medicine, St Louis, 1943. Licensed in California in 1948. Dr Mundy was a member of the Kern County Medical Society.

OLDS, JOHN W., San Diego. Died April 29, 1983, in San Diego, aged 74. Graduate of Rush Medical College, Chicago, 1936. Licensed in California in 1940. Dr Olds was a retired member of the San Diego County Medical Society.

PLATE, AGNES G., San Francisco. Died May 4, 1983, in San Francisco, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr Plate was a retired member of the San Francisco Medical Society.

REIMER, FRANK N., Patterson. Died February 28, 1983, in Patterson of cancer, aged 66. Graduate of Duke University School of Medicine, Durham, NC, 1942. Licensed in California in 1947. Dr Reimer was a member of the Stanislaus Medical Society.

SILVANI, HENRY L., San Francisco. Died Febuary 28, 1983, in San Francisco of myocardial infarct, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr Silvani was a member of the San Francisco Medical Society.

WEVER, GEORGE KUHN, Stockton. Died November 26, 1982, in Stockton of bone cancer, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr Wever was a retired member of the San Joaquin County Medical Society.

Utah State Medical Association

BECK, NORMAN RUSSELL, Salt Lake City. Died July 15, 1983, in Salt Lake City, aged 70. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1937. Licensed in Utah in 1948. Dr Beck was a member of the Salt Lake County Medical Society.

CALL, RICHARD A., Provo. Died May 29, 1983, in Provo, aged 62. Graduate of the University of Utah College of Medicine, Salt Lake City, 1944. Licensed in Utah in 1945. Dr Call was a member of the Utah County Medical Society.

LINDSAY, AUGUST VAN ORMAN, Provo. Died June 13, 1983, in Provo, aged 44. Graduate of the University of Utah College of Medicine, Salt Lake City, 1965. Licensed in Utah in 1966. Dr Lindsay was a member of the Utah County Medical Society.

ROBINSON, ROY W., Price. Died June 15, 1983, in Price, aged 82. Graduate of Washington University School of Medicine, St Louis, 1925. Licensed in Utah in 1926. Dr Robinson was a member of the Carbon County Medical Society.

SMITH, SILAS S., Salt Lake City. Died April 23, 1983, in Salt Lake City, aged 83. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1924. Licensed in Utah in 1925. Dr Smith was a member of the Salt Lake County Medical Society.

Washington State Medical Association

BROWN, JOHN L., Lynden. Died October 24, 1982, aged 62. Graduate of the University of Oregon Medical School, Portland, 1944. Licensed in Washington in 1948. Dr Brown was a member of the Whatcom County Medical Society.

BURKE, DONALD RUSSELL, Renton. Died March 5, 1983, in Renton, aged 57. Graduate of the Creighton University School of Medicine, Omaha, 1948. Licensed in Washington in 1948. Dr Burke was a member of the King County Medical Society.

DEPREE, JAMES F., Seattle. Died October 30, 1982, in Seattle, aged 79. Graduate of Rush Medical College, Chicago, 1931. Licensed in Washington in 1946. Dr DePree was a retired member of the King County Medical Society.

DILLON, ROLL NEWELL, Seattle. Died February 21, 1983, in Palm Springs, Calif. aged 82. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1927. Licensed in Washington in 1928. Dr Dillon was a retired member of the King County Medical Society.

GRIEVE, WILLIAM E., Spokane. Died April 14, 1983, in Spokane, aged 84. Graduate of the University of Oregon Medical School, Portland, 1926. Licensed in Washington in 1928. Dr Grieve was a retired member of the Spokane County Medical Society.

JAQUETTE, WILLIAM A., Bellevue. Died February 12, 1983, in Redmond, aged 72. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1936. Licensed in Washington in 1946. Dr Jaquette was a retired member of the King County Medical Society.

KINZIE, RALPH VERNON, Tonasket. Died May 2, 1983, in London, aged 70. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1942. Licensed in Washington in 1946. Dr Kinzie was a retired member of the Okanogan County Medical Society.

KNUTH, WARREN P., Seattle. Died March 12, 1983, in Atascadero, Calif, aged 59. Graduate of the University of Washington School of Medicine, Seattle, 1953. Licensed in Washington in 1959. Dr Knuth was a former member of the King County Medical Society.

LEFOR, FRANK G., Yakima. Died February 9, 1983, in Yakima, aged 79. Graduate of the Creighton University School of Medicine, Omaha, 1932. Licensed in Washington in 1933. Dr LeFor was a retired member of the Yakima County Medical Society.

SCHUTT, RAY L., Bremerton. Died March 17, 1983, in Bremerton, aged 93. Graduate of the University of Minnesota Medical School, Minneapolis, 1917. Licensed in Washington in 1918. Dr Schutt was a retired member of the Kitsan County Medical Society.

TUCKER, FREDERICK A., Langley. Died April 3, 1983, in Seattle, aged 78. Graduate of the University of Louisville School of Medicine, 1931. Licensed in Washington in 1932. Dr Tucker was a retired membe of the King County Medical Society.

VAN ARSDEL, PAUL P., SR, Seattle. Died January 13, 1983, aged 82. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1926. Licensed in Washington in 1932. Dr Van Arsdel was a retired member of the King County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

OCCUPATIONAL SKIN DISEASE—Robert M. Adams, MD, Clinical Professor, Department of Dermatology, School of Medicine, Stanford University, Stanford, Calif. Grune & Stratton, Inc., 111 Fifth Ave., New York, NY 10003, 455 pages, $69.50.

Dr Adam's new book contains a wealth of useful information about a subject that dermatologists confront daily. His earlier treatise, entitled *Occupational Contact Dermatitis,* (1969) dealt primarily with the narrowed subject of contact dermatitis. This present work, although mainly concerned with contact dermatitis, expands into many other areas of work-related cutaneous disease and contains more than 200 additional pages of information. Special chapters by guest authors deal superbly with contact urticaria, occupational nail disorders and medicolegal aspects of occupational cutaneous problems. Up-to-date facts about occupational skin diseases are difficult to find in the literature. This text proved to be very well referenced, which was refreshing.

New information abounds throughout the book. The chapter on acne leads the reader through the days when "oil acne" was common through the newer findings associated with dioxin. Occupational skin cancer is similarly dealt with from Percivall Pott's observation regarding scrotal cancers in chimney sweeps through the latest effects of ionizing radiation in industry. Dr Adams states that even though dangerous exposure to radiation has been decreased in medicine the hazards have broadened in industry. The industrial uses of ionizing radiation include "curing plastics, sterilizing foods and drugs, testing metals and manufacturing color televisions." Both localized and generalized radiation injury can be seen. Mycosis fungoides may occur more frequently in persons who work in construction and manufacturing. The Food and Drug Administration has banned methyl methacrylate, but butyl and ethyl methacrylate probably will produce as much of a problem with "sculptured nails" because of their similar chemical structure. "Copy paper" dermatitis is due to a diazonium compound in the paper used by the copier. Substitution of an electrostatic copy method, such as used by IBM or Xerox, will alleviate the problem. These are but a few of the many useful new points of information found in this delightful text.

Besides numerous useful tidbits of information that can be put to instant use by practitioners, academicians and researchers, Dr Adams has given us an approach to dealing with occupational medicine in a very effective manner. First he provides a very complete form for data collecting which can easily be adapted to clinical practice if an occupational origin for skin disease is suspected. The tools of a dermatologist used in these evaluations are briefly reviewed (the use of a potassium hydroxide mount, fungal cultures, bacterial cultures, biopsy, patch testing and clinical photographs are mentioned). Patch testing is dealt with in detail. The correct method for inspecting a manufacturing plant in which workers have dermatologic problems without offending the management is tactfully dealt with. The medicolegal aspects of occupational disease and the role of governmental agencies are very thoroughly and clearly explained. Treatment, prevention and rehabilitation of patients are covered in a chapter devoted to these subjects. A very complicated process, the approach to an evaluation of occupational disease, is covered beautifully.

A few areas of this book I particularly liked were the section on patch test chemicals and suggested concentrations for patch testing, the listed sources of skin cleansers, protective clothing and creams and hypoallergenic gloves and boots, the trade names for numerous rubber chemicals and the descriptions of various occupations along with the irritants and allergens encountered in each. Numerous other areas such as the section on plants were also interesting, clear, concise and helpful. I found only one small mistake in the section on nails. Beau's lines were described as white transverse lines rather than transverse depressed grooves—a very small criticism for an extremely well done and useful text.

LEONARD J. SWINYER, MD
Assistant Clinical Professor of Dermatology
University of Utah School of Medicine
Salt Lake City

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DISEASES OF THE GASTROINTESTINAL TRACT AND LIVER—David J. C. Shearman, PhD, MBChB, FRCP (Ed), FRACP, Professor of Medicine, University of Adelaide; and Niall D. C. Finlayson, PhD, MBChB, MRCP (Lond), FRCP(Ed), Consultant Physician, The Royal Infirmary, Edinburgh and Honorary Senior Lecturer, Department of Therapeutics and Clinical Pharmacology, University of Edinburgh, Edinburgh. Churchill Livingstone, 1560 Broadway, New York, NY 10036, 1982. 974 pages, $79.00.

This is a comprehensive textbook on gastroenterology and hepatology by two authors, one from Edinburgh and the other from Adelaide; they have written most of the chapters themselves. Seven chapters were written by surgeons and a specialist on tropical diseases. This makes for very pleasant reading, the style being even throughout the text. The text is arranged in a pragmatic, practice-oriented fashion. The book is lavishly illustrated; the references are carefully selected, recent and critically annotated.

The authors start out with four chapters on gastroenterological procedures. A critical appraisal of the limitations of the methods is missing; the authors still list colonoscopy preparation with mannitol which is well known to be dangerous; this is only mentioned pari passu. A chapter each is devoted to the mouth and the esophagus; seven chapters are devoted to the stomach and five to the small intestine. A surgeon's contribution then covers the acute abdomen and intestinal ischemia. Nineteen chapters are devoted to the liver. Some current controversies, such as penicillamine treatment of primary biliary cirrhosis, are insufficiently addressed. The pancreas, with only one chapter, is treated rather too briefly. The book concludes with eight chapters on the colon, stomal care and anorectal conditions.

Most chapters are preceded by some considerations of pathophysiology. This again is practice-oriented and, due to the limited space, often oversimplified. However, the excellent referencing will guide the reader on the right track.

This book will be valuable to internists and family physicians. It should be available to housestaff and medical students as a reference.

JUERG REICHEN, MD
Assistant Professor of Medicine
University of Colorado Medical School

Cholecystitis in Teenage Girls

BRUCE ADYE, MD, *and* JOHN A. RYAN, Jr, MD, *Seattle*

Cholecystectomy was carried out in 17 teenage girls for cholecystitis at Virginia Mason Hospital, Seattle, between 1971 and 1980. The incidence increased with increasing age. Gallbladder disease was associated with recent pregnancy or birth control pill use (71%), obesity (65%) and family history of gallbladder disease (47%). All but one patient had at least one of these risk factors. No patient had congenital anomalies, blood dyscrasias or other underlying illness. Patients most commonly had recurrent attacks of abdominal pain; seven had symptoms for more than six months. Although the clinical presentations were often mild, six patients had jaundice, three had chemical pancreatitis, one had hemorrhagic pancreatitis, one had pancreatic pseudocyst and abscess and one had a common duct stone. One patient had cholesterosis and 16 had cholelithiasis. All patients were cured by operation. During the same time period, only two boys, both aged 14 years, nonobese and with no family history of gallbladder disease, underwent cholecystectomy, both for acalculous cholecystitis.

Biliary tract disease frequently occurs in women, often associated with obesity and parity. Its occurrence in children, though less frequent, is also well recognized. Pigment stones are often found in children, associated with hemolytic disorders, systemic infections or congenital biliary anomalies. The clinical presentation of biliary disease in teenagers is less well recognized. Is it more similar to that of the pediatric or of the adult population? To better define cholecystitis in teenagers, we did a retrospective study of teenage patients who underwent cholecystectomy for cholecystitis at Virginia Mason Hospital, Seattle.

Methods and Patients

The charts of all patients aged 13 to 19 who had cholecystectomy for cholecystitis at Virginia Mason Hospital between 1971 and 1980 were reviewed. Nineteen patients fit this category, 17 girls and 2 boys. The charts of the female patients were then further analyzed for clinical features, radiographic and laboratory results, treatment and pathologic findings.

Results

Seventeen girls between the ages of 13 and 19 underwent cholecystectomy at Virginia Mason Hospital between 1971 and 1980. There were 15 white and 2 black patients. The youngest was 15 years old and the incidence was found to increase with age. Most patients were between 18 and 19 years of age (Figure 1).

Several well-recognized risk factors for gallbladder disease were found in the teenage girls. Gallbladder disease was associated with recent pregnancy (within the past nine months) or birth control pill use in 12 of 17 (71%) (Figure 2). Obesity, as defined by body weight in excess of 15% of normal weight for height and age, was seen in 11 of 17 (65%) (Figure 3).* Of these 11 obese girls, 2 had mild obesity (115% to 125% of ideal body weight), 5 had moderate obesity (125% to 140% of ideal) and 4 had extreme obesity (more than 140% of ideal). The mean percentage of excess weight in the obese teenage girls was 41%. A family history for gallbladder disease was found in 8 of 17 (47%) (Figure 4). Of the 17 girls, 16 (94%) had at least one risk factor (Figure 5), 13 (76%) had at least two risk factors but only 2 (12%) had all three risk factors. Table 1 summarizes these clinical features for all of the patients.

Many of the risk factors classically associated with gallstones were not found. None of the girls had congenital biliary anomalies, hemolysis, cirrhosis, diabetes mellitus or other severe underlying disease.

The patients most commonly presented with recurrent attacks of epigastric and right upper quadrant pain, frequently associated with tenderness and nausea. Seven patients had intermittent symptoms for more than six

* Values for the normal weight at a specific age and height were obtained from Table A-10 in the appendix of Schneider, Anderson and Coursin's book, *Nutritional Support of Medical Practice*.[1]

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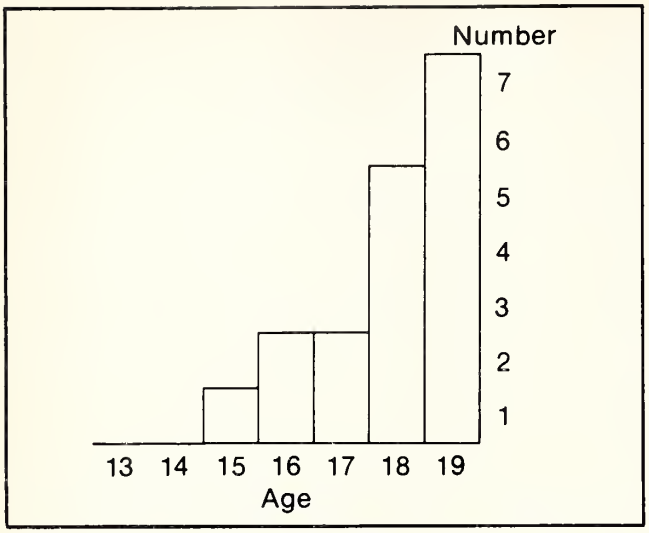

Figure 1.—Age of girls undergoing cholecystectomy.

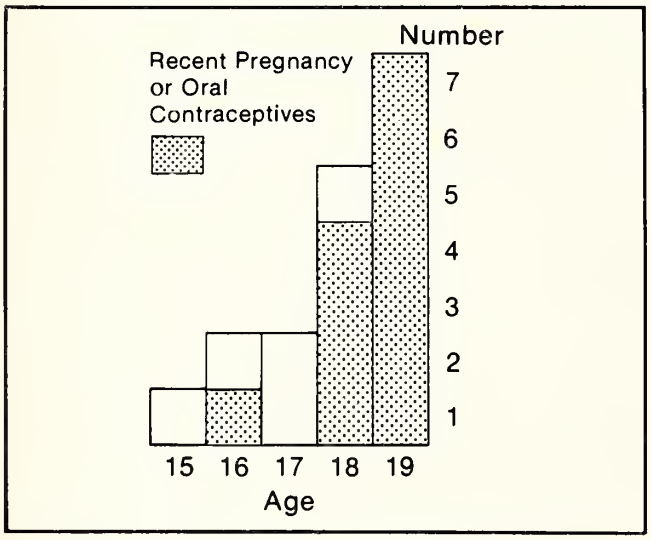

Figure 2.—Pregnancy or oral contraceptive use in teenage girls undergoing cholecystectomy.

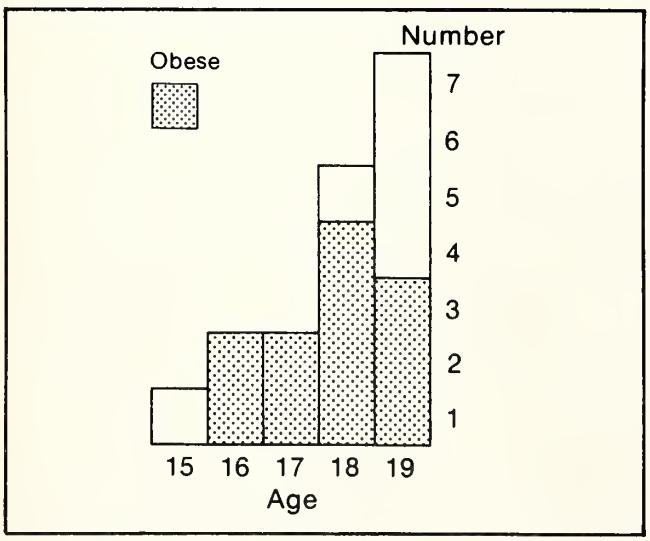

Figure 3.—Obesity in teenage girls undergoing cholecystectomy.

months. Although the clinical presentations were relatively mild, six patients had jaundice, three had chemical pancreatitis, one had hemorrhagic pancreatitis, one had pancreatic pseudocyst and abscess and one had choledocholithiasis. Sixteen patients had cholelithiasis and one had cholesterosis. All patients were cured by operation.

During the same ten-year period, only two teenage boys underwent cholecystectomy. Both boys were aged 14, nonobese and had no family history for gallbladder disease. Acalculous cholecystitis was found in both cases.

Discussion

The clinical presentation of these teenage girls with cholelithiasis was similar to that of adults. The high percentage of female patients among young people with cholelithiasis has been observed previously. Calabrese and Pearlman reported the cases of 33 patients with gallbladder disease who were below the age of 21

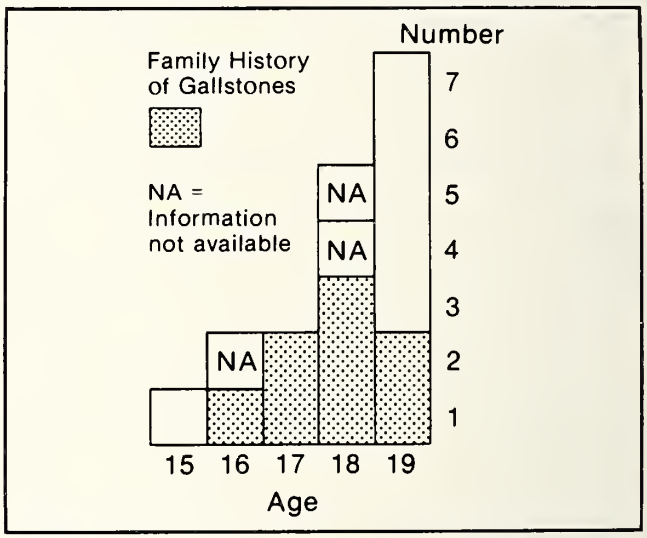

Figure 4.—Family history of gallstones in teenage girls undergoing cholecystectomy.

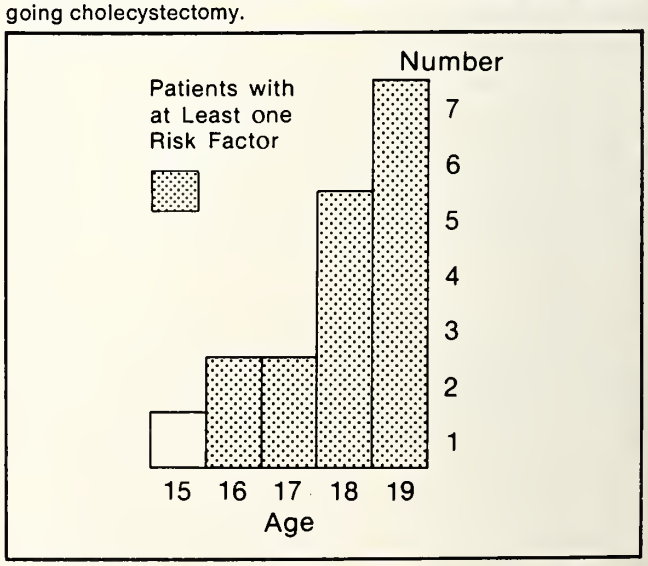

Figure 5.—Presence of risk factors in teenage girls undergoing cholecystectomy.

years, all of whom were female.[2] Fosberg found only 27 male patients among 178 younger than 30 years of age who had cholelithiasis.[3] The presenting symptoms of recurrent attacks of right upper quadrant and epigastric pain accompanied by nausea are classic for cholelithiasis. The high incidence of jaundice (35%) in this series concurs with the 30% incidence noted by Sears and co-workers. They thought it due to periductal obstruction of the biliary tree rather than choledocholithiasis, as none of their patients had common duct stones.[4] The high incidence of cases complicated by pancreatitis in this report (24%) differs from most previous reports, which describe few cases of pancreatitis. In this young population the diagnosis is often delayed for months to years after the onset of symptoms, as described by Goodman who reported the cases of 96 patients under 25 years of age and found that 26% had had symptoms for one to five years.[5] This is in agreement with our series in which 41% of the patients suffered their symptoms for more than six months before diagnosis and treatment.

The most impressive feature of our series is the strong association of cholelithiasis in teenage girls with recent pregnancy or birth control pill use, obesity and a family history. Previous reports support these findings. Holcomb and colleagues reported a 65% incidence of pregnancy in the teenage girls with cholelithiasis whom they studied. They found a 33% incidence of obesity but a positive family history in only 7%.[6] Honore described 31 female adolescents who had cholelithiasis and found a 58% incidence of pregnancy and a 55% incidence of obesity. He found family history of gallbladder disease in only 3%.[7] Crichlow and associates found a 42% incidence of prior pregnancy among 31 adolescent girls with cholecystitis, and reported that over half of the patients were obese or had recently dieted to reduce body weight.[8] The incidence of obesity and pregnancy from the present study compares quite closely with those reported above.

The mechanism by which each of these risk factors is associated with cholelithiasis has been established in the adult population. Lithogenic bile is derived from the saturation of bile with cholesterol in solution with bile salts and lecithin. Bennion and Grundy described stone formation occurring in three stages: (1) formation of saturated bile, (2) nucleation or initiation of stone formation and (3) growth of stone to a detectable size.[9] Factors affecting either the bile components or stages of formation influence the production of stones.

Estrogen and progesterone are the agents responsible for the increased incidence of cholelithiasis in association with pregnancy and birth control pill usage. Estrogen increases bile cholesterol saturation by decreasing the absolute size of the total bile salt pool, especially the chenodeoxycholic acid portion. Both estrogen and progesterone have been shown to result in smooth muscle relaxation and impaired gallbladder emptying, which contributes to excess cholelithiasis by allowing stone growth.[10]

Obesity is associated with lithogenic bile due to supersaturation with cholesterol, which results from excessive hepatic secretion of cholesterol. Mabee and co-workers reported that biliary cholesterol secretion was related to total body weight.[11] The activity of

TABLE 1.—*Clinical Summary of 17 Cases in Which Cholecystectomy Was Done for Cholecystitis in Teenage Girls*

Patient	*Age*	*Body Weight (lbs)*	*% Ideal Body Weight*	*Oral Contraceptives*	*Pregnancy*	*Family History*
1	15	113	115	No	No	No
2	16	166	130	Unknown	1 month postpartum	Unknown
3	16	254	185	No	No	Grandmother
4	17	156	141	No	No	Mother, Grandmother
5	17	190	135	No	No	Mother, 2 siblings, Grandmother
6	18	123	108	No	7 months postpartum	Unknown
7	18	176	131	Yes	1 month postpartum	Grandmother
8	18	171	128	Yes	6 months postpartum	Mother
9	18	145	107	Yes	No	Unknown
10	18	171	120	No	No	Mother
11	19	218	179	Yes	4 months after elective abortion	No
12	19	107	88	Unknown	9 months postpartum	Mother
13	19	186	146	Yes	9 months postpartum	No
14	19	125	96	No	1 month postpartum	No
15	19	184	136	Yes	No	No
16	19	132	98	Yes	3 months postpartum	Mother
17	19	128	100	Yes	No	No

β-hydroxy-β-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis, varies directly with the amount of food intake and plasma insulin levels, both of which are elevated in obesity.[12] The excessive synthesis and hepatic secretion of cholesterol, induced by obesity, then leads to stone formation by the creation of saturated bile.

The role family history plays in cholelithiasis is less well understood. That cholelithiasis shows familial aggregations is well accepted. Jackson and Gay studied 100 consecutive cases of cholelithiasis and found a positive family history in 33%, from which they proposed a sex-linked dominant-inheritance pattern showing varying penetrance.[13] Danzinger and associates showed that younger sisters of women with cholelithiasis had bile that was more highly saturated with cholesterol than the younger sisters of non-gallstone-bearing controls, suggesting that the inherited tendency toward lithogenic bile is due to increased bile cholesterol saturation. They postulated that each person has a polygenic genetic predisposition toward gallstone formation and that an early age of onset of gallstone disease reflects a greater polygenic predisposition. Thus, patients who are young when cholelithiasis develops are more likely to have affected relatives.[14]

Although cholecystitis is of low incidence in teenage girls, it can result in great morbidity, as in our study in which six (35%) of the teenage girls with cholelithiasis had complicated cases. In one obese 16-year-old from this series who was three weeks postpartum, severe biliary pancreatitis developed. A large pancreatic pseudocyst, a subphrenic abscess and severe upper gastrointestinal tract bleeding further complicated her course. Only after three separate surgical procedures did her abdominal problems resolve.

Summary

Cholecystitis in teenage girls often occurs in the setting of recent pregnancy or birth control pill use, obesity and family history of gallbladder disease. Clinical presentation is similar to that in adults. Recognition of these facts, combined with cholecystectomy, will lead to earlier diagnosis and therapy and prevent serious complications.

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Use of Immunologic Markers in Obscure Hematologic Disease

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Tumor cells from two patients with very different clinical diseases were evaluated using immunologic techniques. The first patient had a persistent T-cell lymphocytosis and other symptoms suggestive of T-cell malignancy. She also had an adnexal mass. Following surgical excision, the mass was identified as a benign teratoma that contained thymic tissue. The T-cell lymphocytosis subsided following removal of the mass. The second patient had leukemia, the cells of which were morphologically identified as myelomonocytic. Surface marker studies, however, showed the presence of monoclonal surface immunoglobulins. Enzymatic digestion of the cells showed that the antibodies were cytophilic and not produced by the tumor population. These studies emphasize the value of immunologic techniques in characterizing tumor cells.

Evaluation of lymphocyte surface markers and substructures in lymphoproliferative disorders has become routine in many institutions. Typically these techniques involve such procedures as identifying T lymphocytes by E rosetting, B lymphocytes by EAC rosetting and surface immunoglobulins by fluorescence microscopy. These, along with the use of electron microscopy and immunoperoxidase evaluation of fixed tissue sections, often provide valuable insight as to the malignant cell of origin. We describe the use of these techniques in two cases in which the diagnosis of lymphoproliferative disease was a prime consideration.

Materials and Methods

Lymphocyte Preparation

Peripheral blood and bone marrow aspirates were collected in parenteral-grade heparin (Lipo-Hepin, Riker Laboratories, Inc, Northridge, Calif) and incubated with iron carbonyl (Atomergic Chemetals Co, Cable Place, NY) for 30 minutes at 37°C to facilitate removal of phagocytic cells. Solid tissues were minced into RPMI 1640 and forced through a fine-mesh wire screen. The lymphocytes from all samples were separated by centrifugation on Ficoll-Hypaque gradients.[1]

Surface Marker Studies: Sheep Erythrocyte Rosette (E Rosette) and EAC Rosettes

The procedure used is essentially that described by MacKenzie and Paglieroni.[2] A total of 200 viable lymphocytes was counted in a hemacytometer and those cells with three or more adherent erythrocytes were considered E rosette-positive. Aliquots of all preparations were cytocentrifuged, stained with Wright-Giemsa stain and evaluated microscopically.

Surface Immunoglobulin Evaluations

The technique used is essentially that of Paglieroni and MacKenzie.[3] In all, 200 viable cells were counted and the percentage of fluorescent cells determined using a Leitz Laborlux 12 fluorescent microscope.

Cells were fixed in modified Karnovsky's solution and evaluated according to standard electron microscopic procedures.[4,5]

Cytochemical and Histologic Stains

Cells were stained for specific and nonspecific esterase, periodic acid-Schiff (PAS) and myeloperoxidase using routine procedures. Tissue sections were fixed using B5 formalin and embedded in paraffin for sectioning and staining with hematoxylin and eosin. Immunoperoxidase study was done essentially as described by Sternberger.[6]

Trypsinization Studies

Aliquots of Ficoll-Hypaque-purified lymphocytes in RPMI 1640 supplemented with 2 mmol of glutamine and 15% pooled human type AB serum (decomplemented) were incubated with 2.5 mg per ml of trypsin

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for 30 minutes at 37°C.[7] The cells were gently washed with phosphate-buffered saline. Following incubation at 37°C for 24 hours, the cells were reexamined for the presence of surface immunoglobulins by the direct fluorescent technique as described above.

Patients

Report of Cases

CASE 1. The patient, a 32-year-old woman, was referred to our institution because of pruritus, urinary retention and lower extremity weakness for a week. On physical examination there was a right adnexal mass; there were no skin lesions, lymphadenopathy or hepatosplenomegaly, and there were bilateral sixth nerve palsy, lower extremity weakness and absent lower extremity reflexes. There were no pathologic reflexes. A diagnosis of encephalomyelitis was made, based on a spinal fluid protein value elevated at 165 mg per dl (negative for multiple sclerosis-associated IgG), a cell count of 268 mononuclear cells per μl and diffuse disorganization seen on the electroencephalogram. Her initial hemogram and chemistry panel showed no abnormalities. A pelvic ultrasound study confirmed the presence of a 5 by 8 cm cystic right adnexal mass. The pruritus was extremely severe. The patient was discharged two months later following significant recovery of neurologic function and rehabilitation, with a laparotomy planned for the near future. Results of the hemogram done at discharge were normal.

Six weeks later she noted "spots" on her legs consisting of multiple erythematous, nonblanching punctate lesions, 0.25 cm in diameter, on the dorsum of both feet. A skin biopsy specimen showed mild perivascular lymphocytic infiltration. The intense pruritus persisted and lymphocytosis was first noted in the blood. There were no other skin lesions, lymphadenopathy or splenomegaly. Bone marrow examination showed numerous aggregates of morphologically mature lymphocytes. The differential diagnosis of a lymphoproliferative disorder versus a hyperimmune reaction to the viral agent of the encephalitis was entertained and specimens of peripheral blood and bone marrow were submitted for specific lymphocyte studies. No intranuclear or intracytoplasmic viral inclusions were identified. Viral cultures and serologic testing failed to identify an etiologic agent. A laparotomy was done.

CASE 2. The patient, a 40-year-old woman, was referred to the University of California, Davis, Medical Center with a diagnosis of probable B-cell lymphoma with IgGκ marking cells. Three months before admission she had noted increased fatigue. A labial abscess developed two months later. Two weeks before admission she had swollen gums, sore throat and night sweats. At that time a hemogram showed severe anemia, with a platelet count of 30,000 per μl; the leukocyte count was 30,000 per μl with monoblastoid and mononuclear-appearing cells. Specimens of bone marrow aspiration and lymph node biopsy showed infiltration of mononuclear cells, with IgGκ immunoglobulins on the surface of cells from the node.

On transfer to hospital she was febrile, in a toxic state and had gingival hyperplasia and multiple cervical lymph nodes up to 3 cm in diameter. Hepatosplenomegaly was not noted. Her hemoglobin was 8 grams per dl, platelet count 30,000 per μl and her leukocyte count was 80,000 per μl. Morphologically, most cells appeared to be monocytes. Repeat aspiration of bone marrow showed replacement by malignant mononuclear cells. The differential diagnoses were acute myelomonocytic leukemia versus lymphoma. Specimens of peripheral blood and bone marrow were submitted for special stains and immunologic studies.

Results, Case 1

Lymphocyte Surface Marker Studies

Table 1 shows the results of sequential surface marker evaluations done on specimens of peripheral blood, bone marrow and ovarian mass. All tissues examined showed a striking increase in cells that formed rosettes at 4°C ($E^{4°}$) and, with the exception of the peripheral blood from week 13, an increase in the number of cells forming E rosettes at 37°C ($E^{37°}$). Further, the ovarian mass had no mononuclear populations that exhibited either surface immunoglobulins or a receptor for the third complement component. The mass did, however, have 46% of the cells forming E rosettes at 4°C and 78% formed E rosettes at 37°C. Bone marrow lymphocytes obtained during week 2 showed a pronounced increase of $E^{4°}$-positive cells (42%) and a modest elevation in $E^{37°}$ (11%). Figure 1 shows the absolute lymphocytosis seen three weeks before the surgical procedure (4,260 lymphocytes per μl), one week before (3,465 lymphocytes per μl), ten days after (3,132 lymphocytes per μl) and eight weeks after operation (3,150 lymphocytes per μl). The absolute number of E-rosetting cells at 4°C seen in Figure 1 are as follows: 2,811

TABLE 1.—*Lymphocyte Surface Markers in Case 1*

Time	Specimen	Rosettes %			Surface Immunoglobulins %						
		$E^{4°}$	$E^{37°}$	EAC	Polyvalent	G	A	M	D	κ	λ
Week 1	PB	66	9	1	8	3	1	3	1	5	4
2	PB	75	22	0	8	4	2	5	3	4	3
5.5	PB	83	6	11	7	2	1	2	1	3	3
13	PB	73	4	12	10	2	1	2	1	3	3
Month 2	BM	42	11	4	10	10	2	3	1	9	3
4	OM	46	78	0	1	0	0	0	0	0	0
Control	PB	55	2	21	20	4	3	8	8	12	8
Control	BM	11	2	30	35	10	1	15	11	15	7

PB = peripheral blood, BM = bone marrow, OM = ovarian mass

lymphocytes per μl three weeks before, 2,598 lymphocytes per μl one week before, 2,599 lymphocytes per μl ten days after and 2,299 lymphocytes per μl eight weeks after operation. The following absolute number of lymphocytes form E rosettes at 37°C: 383 lymphocytes per μl three weeks before, 763 lymphocytes per μl one week before, 187 lymphocytes per μl ten days after and 31 lymphocytes per μl eight weeks after surgical procedure.

Bone Marrow Cytology

Examination of bone marrow aspirates showed an active marrow, with 65% of the marrow containing appropriately maturing blood cells. Megakaryocytes were mature and present in normal numbers. The granulocytic and erythrocytic series were active and showed normal maturation. The granulocyte-erythrocyte ratio was normal.

Some areas of the marrow showed a lymphocytic infiltration consisting of some young, but mostly mature, cells. No lymphoblasts were seen. Stainable iron was present in normal amounts. The final impression was that of marrow showing a lymphocytic infiltrate.

Ovarian Mass Pathology

Gross examination of the ovarian tumor specimen showed a yellow-white mass having a rubbery consistency; a representative sample was fixed in B5 formalin. Microscopic examination of multiple sections stained with hematoxylin and eosin showed the neoplasm to be composed of benign elements of lymphoid, cartilaginous and mucosal tissue. Some of the mucosa was thin and attenuated, showing areas of mucin production. The lymphoid tissue was lobular and had a thymic cortical and medullary delineation (Figure 2-A). Well-formed Hassall's corpuscles were not identified. A small focus of pale epithelial cells with a parathyroid morphology was noted in the thymic tissue (Figure 2-B). There was a moderate cortical hyperplasia of the thymus and pale macrophages scattered throughout the cortex (Figure

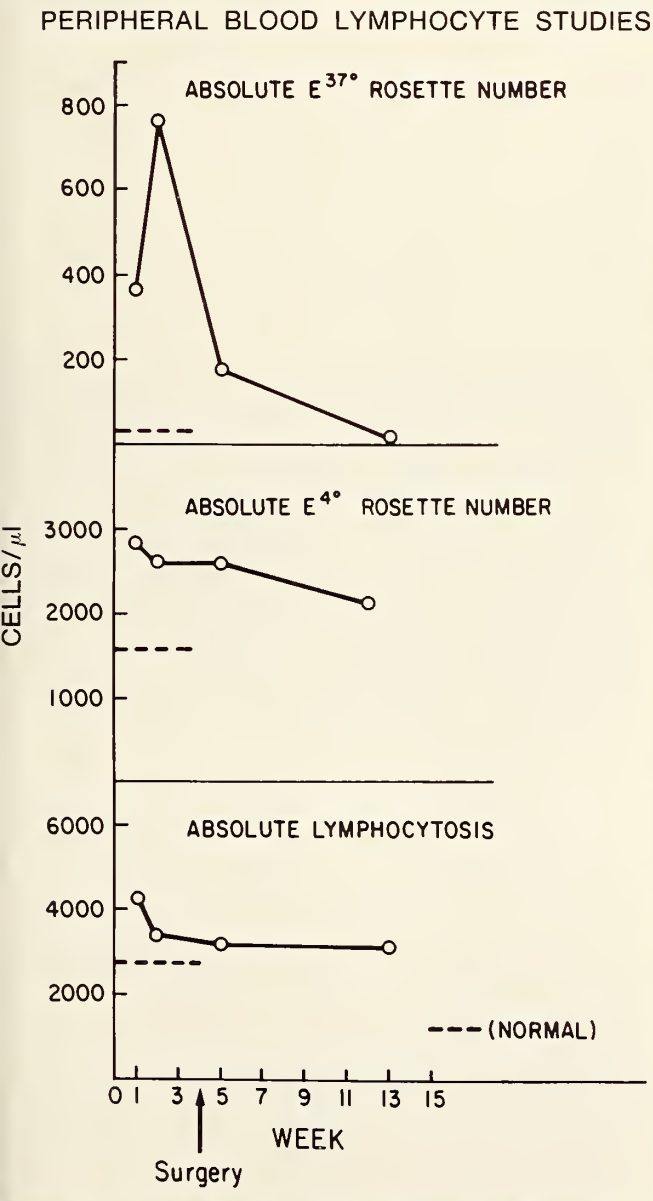

Figure 1.—Absolute peripheral blood lymphocyte values on cells from case 1. Cells had been evaluated for rosette-forming capability with sheep erythrocytes at 37°C ($E^{37°}$) and 4°C ($E^{4°}$).

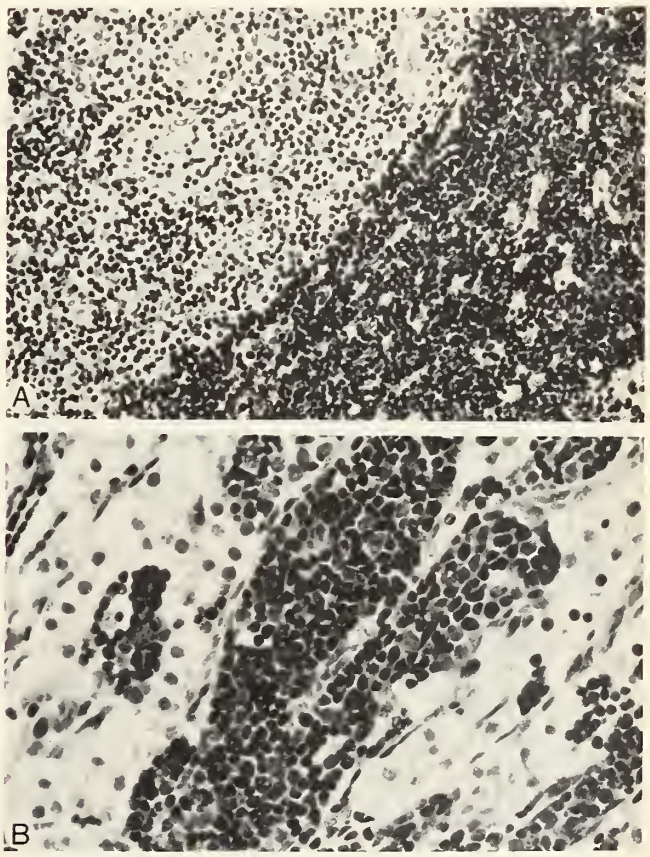

Figure 2.—**A,** Low-power magnification (reduced from ×40): Hematoxylin-eosin-stained section of benign ovarian teratoma from case 1. Compactly arranged cells are seen in the thymic cortex to the right and on the left loosely arranged cells are found in the thymic medulla. **B,** High-power magnification (reduced from ×100). Cords of pale epithelial cells with parathyroid morphology are found separating thymic lymphocytes.

2-B). In occasional medullary fibrous cords a few myeloid cells were present. No malignant elements were identified. The pathologic diagnosis was right ovarian teratoma, benign.

Results, Case 2

Morphology and Cytochemistry

Studies of peripheral blood (Figure 3-A) and bone marrow (Figure 3-B) showed infiltration by malignant cells thought by various observers to be monocytic. Results of PAS, myeloperoxidase and specific esterase stains were negative. In all, 65% of the cells stained with nonspecific esterase.

Electron Microscopy

Low-magnification electron micrographs (Figure 4-A) show the malignant cells. Nuclei are irregular in profile, containing small amounts of diffusely clumped chromatin and prominent nucleoli. The cytoplasm is abundant and contains mitochondria and large numbers of electron-dense granules. At higher magnification (Figure 4-B) the nuclear structure and nucleoli are more evident. One cell contains a prominent Golgi region. The cytoplasmic granules are varied and morphologically show a nonlymphoid structure. Some granules are very similar to those seen in monocytes.

Immunoperoxidase

Immunoperoxidase studies done on bone marrow showed only scattered cells containing IgG$_\kappa$. Most of the cells, however, stained strongly for lysozyme.

Surface Marker and Trypsinization Studies

Peripheral blood mononuclear cells were analyzed for surface markers in our laboratory and that of another facility (Tables 2 and 3). Comparable data were obtained on peripheral blood values from both institutions. Results from both laboratories showed that the number of $E^{4°}$-rosetting cells in the peripheral blood was greatly reduced (30% and 21%). In addition, both sets of data show a large population of cells that stained for IgG (37% and 58%) and κ (42% and 49%). Evaluation of Ficoll-Hypaque-separated bone marrow cells showed 53% IgG and 40% κ-bearing cells. Following trypsinization and incubation of the gradient-purified mononuclear cells, the presence of surface immunoglobulins was as follows: cells bearing polyvalent immunoglobulins were reduced from 54% to 2%, IgG from 58% to 2% and κ from 49% to 2%.

Discussion

These two patients had very different clinical diseases. In each it was necessary to consult the clinical immunology laboratory for assistance in diagnosis.

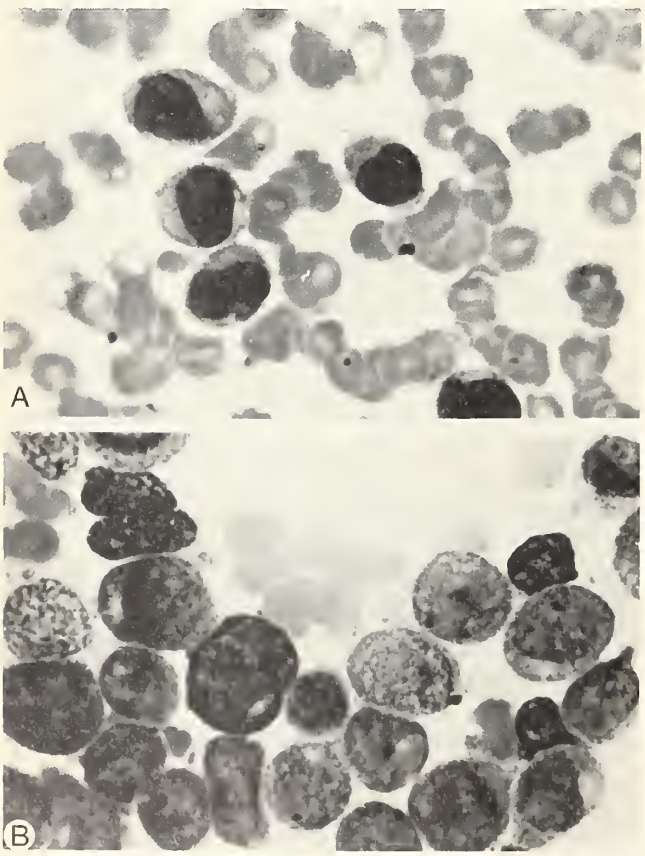

Figure 3.—A, Wright-Giemsa-stained peripheral cells from case 2. (Reduced from magnification ×250). **B,** Wright-Giemsa-stained bone marrow aspirate from case 2. (Reduced from magnification ×250.)

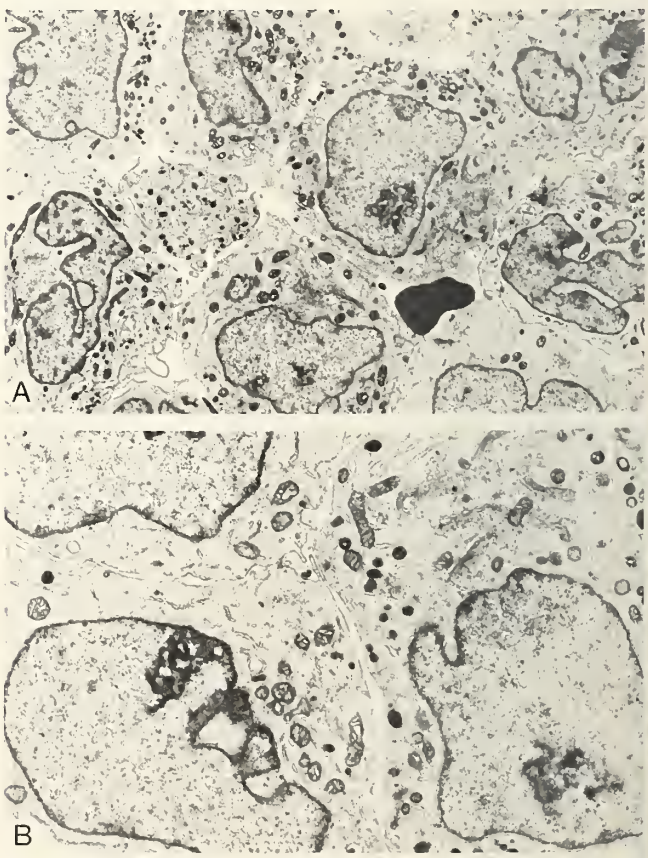

Figure 4.—A, Electron micrography of peripheral cells from case 2. (Reduced from magnification ×4,700.) **B,** Electron micrography of peripheral cells from case 2. (Reduced from magnification ×10,000.)

TABLE 2.—*Lymphocyte Surface Markers, Case 2*

	Rosettes %			Surface Immunoglobulins %						
Specimen	$E^{4°}$	$E^{37°}$	*EAC*	*Polyvalent*	*G*	*A*	*M*	*D*	κ	λ
Patient										
BM	3	<1	7	55	53	1	0	0	40	12
PB	30	<1	31	44	37	1	2	3	42	14
Control										
BM	11	<1	30	35	10	1	15	11	15	7
PB	55	<1	21	20	4	3	8	8	12	8

BM = bone marrow, PB = peripheral blood

TABLE 3.—*Effects of Trypsin on Peripheral Blood Lymphocyte Surface Markers in Case 2*

	Percent Rosettes			Percent Surface Immunoglobulins						
Treatment	$E^{4°}$	$E^{37°}$	*EAC*	*Polyvalent*	*G*	*A*	*M*	*D*	κ	λ
None	21	2	41	54	58	0	2	1	49	2
Trypsin*	..	..	..	2	2	..	..	..	2	..

* Cells treated with trypsin, incubated, then reexamined.

The first patient had a severe, life-threatening viral disease from which she was recovering when significant lymphocytosis developed. The lymphoid aggregates in the marrow, the skin lesions and the intense pruritus raised the question of malignant T-cell disease. This impression was strengthened by the finding of increased levels of $E^{4°}$ and $E^{37°}$ markers, confirming T-cell proliferation. It was expected that the right adnexal mass would be a T-cell lymphoma. Pathologically, it was a benign teratoma that included a sizable amount of normal-appearing thymic tissue, which was confirmed by histologic and immunologic studies. The presence of thymic tissue in a teratoma, though rare, has been observed by other investigators.[8] The peripheral blood lymphocytosis persisted for several weeks postoperatively. It is known that T cells are long lived, and the persistence of the $E^{4°}$ markers suggests that the lymphocytosis was of T cells. The pronounced drop in $E^{37°}$ postoperatively could be attributed to loss of functional thymic mass in the teratoma. It is known that thymic cells form E rosettes at both 37°C and 4°C, whereas mature unstimulated peripheral T cells rarely form E rosettes at 37°C.

It is not known whether the thymic cells from the teratoma were circulating in the peripheral blood or whether the thymic mass induced systemic T-cell proliferation, or both. At present we have elected to observe the patient and not institute therapy for possible T-cell hyperplasia. We speculate that we have seen peripheral blood T-cell proliferation induced by thymic tissue in a benign teratoma. If so, it is of great interest to note that skin lesions and pruritus appear to have been induced by a benign proliferation. Both have disappeared since the operation.

The second patient had a more acute problem. She was referred with a diagnosis of malignant lymphoma with monoclonal antibodies on the cells. Clinically and morphologically she appeared to have an acute myelomonocytic leukemia. The cytochemistry studies showed increased staining with nonspecific esterase and absence of staining with PAS and specific esterase. This suggested monocytic disease, a suspicion strengthened by the finding of serum lysozyme levels 20 times normal. Yet, it was puzzling that the cells marked so strongly with immunoglobulin. The trypsinization studies were invaluable in that they showed that the antibody was cytophilic and not produced by the malignant cells (Table 3). This patient received appropriate therapy for acute myelomonocytic leukemia. Cytophilic antibodies are not commonly identified in this type of leukemia, though polyclonal immunoglobulins have been reported on normal and malignant granulocytes.[9] Cell surface immunoglobulins are not usually investigated in the presence of acute myelomonocytic leukemia.

The monoclonality of the antibody is intriguing. Theoretically, it could represent an antibody directed against a specific leukemic antigen, adhesion of nonspecific antibody to malignant cells bearing very specific immunoglobulin receptors or the presence of a subset of monocytes whose Fc receptor was specific for one immunoglobulin class. Further studies are needed to clarify the significance of this finding.

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Physicians on Mount Everest

A Clinical Account of the 1981 American Medical Research Expedition to Everest

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The American Medical Research Expedition to Everest had a wide variety of medical problems, ranging from leech bites to high-altitude pulmonary edema. Preventive measures, however, such as careful attention to ingesting only pure water and food at the lower elevations and adequate personal hydration, nutrition and rest at extremely high altitude minimized the morbidity suffered by the group. Prophylactic administration of doxycycline was effective in reducing the severity of diarrheal illness in the group. Every member of the expedition suffered upper respiratory tract infections and many other infections, some of which were resistant to all therapy until the patient moved down from high altitude. Despite careful acclimatization, several cases of acute mountain sickness occurred and required descent to a lower altitude for treatment. Frostbite was avoided entirely.

The American Medical Research Expedition to Everest (AMREE), conceived and led by Dr John B. West of the University of California at San Diego, spent August to November 1981 on Mount Everest (Figure 1) in the kingdom of Nepal studying the physiologic responses of humans to extremely high altitude. Ten physicians, nine from the United States and one from Great Britain, took part in this venture,* which was funded by the National Institutes of Health, the American Lung Association, National Science Foundation, American Alpine Club, National Geographic Society, Servier Laboratories (Paris), The Explorers Club, The US Army Research and Development Command and by many private donations. The expedition comprised 21 members in all (not including porters).

Of the ten physicians on the expedition, all climbed to an altitude of 6,300 m (20,700 ft) above sea level, five ascended beyond that to 8,050 m (26,400 ft) and two (Drs Peter Hackett and Chris Pizzo) ascended to the earth's highest point, the summit of Mount Everest, 8,848 m (29,028 ft).

The 1981 American Medical Research Expedition to Everest was the first expedition to earth's tallest mountain dedicated to studying the physiology of humans at the top of the world. While this lofty purpose created high excitement for the trip's scientists, it caused many problems for the physicians charged with caring for the health of the expedition members. Large amounts of scientific gear had to be moved high on the mountain, necessitating extra Sherpa† porters with their attendant health problems, and many of the scientist members had to climb to and remain at extremely high altitudes for prolonged periods in sufficiently good physical and mental condition to conduct research. That the scientific, mountaineering and recreational goals of the expedition were accomplished without the loss of life or limb or without even a medical catastrophe attests to our good luck, good weather and careful attention to details of health care learned on previous expeditions.

The studies we hoped to carry out are shown in Figure 2, with a check mark next to each completed study, indicating that we accomplished nearly everything we set out to do. Three of our members climbed to the summit of Mount Everest, along with two of the Sherpas. We returned from Asia healthy, friends and having enjoyed ourselves. We consider the venture

*The physicians taking part in AMREE were Steven Boyer, David Graber, Peter Hackett, Karl Maret, Chris Pizzo, Frank Sarnquist, Robert Schoene, John West and Robert Winslow from the United States and James Milledge from Great Britain.

†Sherpas are people from the Solu and Khumbu Valleys of Nepal who have traditionally served as high altitude porters, cooks and assistants to Himalayan mountaineering expeditions.

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completely successful. The results of the scientific work will be published in the appropriate journals as they are prepared; this report deals only with the health problems of the expedition.

Preparations

Medical preparation for each member was as outlined in Table 1. A personal first-aid kit was given to everyone (Table 2), and an instruction sheet on the use of the items was issued. Every member was encouraged to arrive at the mountain as physically fit as possible. Medical supplies were assembled in the United States, with all the required supplies donated by the drug and medical supply industries. At the end of the expedition, unused medicines and equipment were donated to several charity-supported hospitals in eastern Nepal.

Figure 1.—Mount Everest. Earth's highest point rises on the left in the photo.

Approaching Mount Everest

The walk from Kathmandu (900 m) to base camp (5,400 m) on the Khumbu Glacier is one of the world's most beautiful treks, and is much frequented by outdoor enthusiasts from around the globe. We, however, set out on August 6, 1981, in the middle of the rainy monsoon period, and thus had the muddy, leech-infested trail to ourselves. Our medical goal on the trail was to avoid "third world ills" by a careful program of simple public health measures aimed primarily at assuring the purity of our food and water. Basic to this program was complete avoidance, in any form, of untreated water and the ingestion of only thoroughly cooked food (or unbroken fruits and vegetables that could be peeled and washed in treated water). In addition we educated and supervised the kitchen Sherpas as to hand washing, food and water handling and washing of dishes. All of the Sherpas who worked in the kitchen received a single dose of mebendazole by mouth to rid them of intestinal parasites.

A major contribution to our public health effort

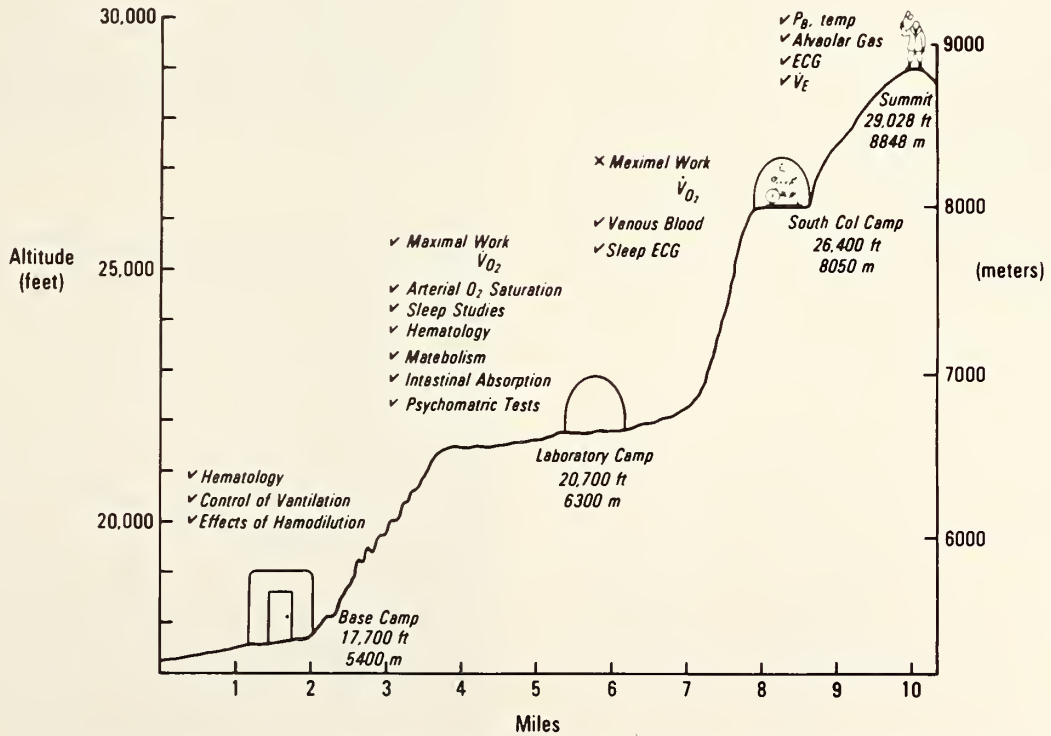

Figure 2.—This diagram of Mount Everest depicts the location of our scientific camps and names the planned studies or measurements. The check marks denote projects completed, the "x" a project that was abandoned. $\dot{V}o_2$ = oxygen uptake, ECG = electrocardiogram, P_B = barometric pressure, $\dot{V}e$ = minute ventilation.

was a water purification system (donated by the Wal-Bro Company of Ann Arbor, Mich) that provided us an immediate supply of potable cold water, a luxury in a country where virtually all water is polluted. This system, which uses an ion exchange resin to iodinate water, included small purifiers for each member to use for treating drinking water along the trail, and large purifiers for the quantity of water needed for cooking, hand washing and dish washing for several dozen people.

TABLE 1.—*Personal Medical Preparations*

History
- Fill out medical questionnaire

Physical Examination
- Including detailed dental and eye examinations

Laboratory Studies
- Blood type
- Complete blood count
- Chest x-ray
- 12-lead electrocardiogram
- Urine analysis
- Tuberculin skin test

Immunizations (up-to-date, recorded on a World Health Organization card)
- Poliovirus vaccine inactivated
- Tetanus toxoid
- Diphtheria antitoxin
- Typhoid vaccine

Prophylaxis
- Hepatitis: Immune globulin, 2 ml given intramuscularly just before leaving the United States
- Diarrhea: Doxycycline (Vibramycin) 100 mg by mouth each day
- Malaria: Not recommended

TABLE 2.—*Contents of Personal First Aid Kits*

- Adhesive tape
- Bandaids
- Aspirin
- Aspirin with codeine, 30 mg
- Diphenoxylate hydrochloride with atropine (Lomotil)
- Flurazepam (Dalmane), 15 mg
- "Cold" tablet (phenylpropanolamine hydrochloride, 50 mg; chlorpheniramine maleate, 8 mg, and isopropamide, 2.5 mg [Ornade])
- Cēpacol throat lozenges (Merrell-National Laboratories, Inc; cetylpyridinium chloride, benzyl alcohol and aromatics in a hard-candy base)
- Dextroamphetamine sulfate (Dexedrine), 5 mg
- Multivitamins
- Safety pins
- Elastic bandage
- Moleskin
- Doxycycline (For those who elected to take it prophylactically)
- Instruction sheet

	Taking Doxycycline N=8		Not Taking Doxycycline N=13	
	Number	(percent)	Number	(percent)
No diarrhea	4	(50)	4	(31)
Mild diarrrea	4	(50)	4	(31)
Severe diarrhea	0	(0)	5	(38)

Figure 3.—Our experience with the use of doxycycline for the prophylaxis of traveler's diarrhea in Nepal.

Figure 4.—Trail companions—the leeches of the Nepalese lowlands.

Doxycycline, along with a report of its efficacy and toxicity, was offered to all the expedition members, but the decision to take the drug was left to each person. Figure 3 shows our experience with diarrheal illness and the efficacy of the prophylactic antibiotic in this situation. Although these data were collected in a non-random, open fashion, they are similar to the results of more rigorous studies[1,2] of the effectiveness of tetracyclines in preventing and ameliorating "turista." In all diarrhea cases that occurred during the expedition, sufferers were urged to tolerate the disease for a day, which in most cases was adequate time for spontaneous recovery. With failure of the "tincture of time" therapy, treatment was begun with metronidazole if *Giardia lamblia* was suspected as the causative agent (diarrhea plus bloating and foul-smelling belching) or a combination of trimethoprim (160 mg) and sulfamethoxazole (800 mg) if the diarrhea was complicated by fever and toxic symptoms. In these cases diphenoxylate hydrochloride with atropine sulfate (Lomotil) was also used for symptomatic relief. Three cases required more than one course of treatment.

A flulike syndrome struck several members during the approach and was treated symptomatically. Many leech bites (Figure 4) were sustained along the trail but only two became infected. Cutter Insect Repellent (Miles Laboratories, Inc, 7123 West 65th St, Chicago, IL 60638) appeared to be an effective leech repellent when used regularly. One infected leech bite, despite antibiotics and intensive local wound care, would not heal and made it impossible for the affected Sherpa to

wear boots, preventing him from working on the mountain.

On the Mountain

The pattern of health problems changed after we reached base camp. Leeches and polluted water were below us and were replaced by the problems of living in the cold, dry, oxygen-poor air of Mount Everest. From base camp on, the preventive medicine program switched emphasis from public health measures to careful attention to three personal health goals. Our aim was to keep the expedition members abundantly hydrated, well fed and adequately rested. We feel the outstanding physical performance of the expedition members, two of whom climbed the final 800 vertical meters on Mount Everest in less than five hours, attested to the success of this program. In addition, the enormous effort made by everyone to remain hydrated, nourished and rested contributed to the relatively few medical problems we encountered.

Figure 5.—Hand infection due to minor trauma.

Figure 6.—Cellulitis resulting from an olecranon bursitis.

Even these measures did not obviate all problems. Sore throat, runny nose and dry, chronic cough affected every member of the expedition. Occasionally these symptoms were disabling, but generally they were only annoying. Colds were treated with a combination of medically unproved maneuvers, including rest, juice, alcohol, vitamin C, cough drops, antihistamines, aspirin and "cold tablets." In cases accompanied by fever, myalgias, purulent sputum or lymphadenopathy, an antibiotic (usually ampicillin) was used.

Infections distant from the respiratory tract were the second most prevalent health problem on the mountain. Nearly every accidental wound, no matter how small, suppurated for a period of time and subsequently healed slowly. (This was not true, however, of the expedition's most frequent wound, that inflicted by the probing venipuncture needle of the specimen-seeking scientists.) Several wounds, particularly of the hands (Figure 5), including the leech bite spoken of earlier, simply did not heal at all until the patient descended to lower altitude. The most frightening infection seen was an olecranon bursitis that rapidly progressed to a cellulitis (Figure 6) involving the entire arm from wrist to shoulder. Resistant to rest, heat and oral antibiotics, the infection was finally brought under control by descent to a lower elevation and antibiotics given intravenously. Several expedition members suffered a syndrome of sore throat, mild fever, tender cervical lymph nodes and malaise. An epidemic of a "glandular feverlike " illness, later identified as caused by an adenovirus, greatly weakened a previous Mount Everest expedition.[3] The exact nature and cause of this problem on our trip was not identified, and recovery was spontaneous with return to lower altitudes. In all, 9 of the 21 members of our expedition suffered significant infections (not including the universal upper respiratory tract troubles). The reason for this high incidence of infection in otherwise fit persons is unclear. The team physicians felt as if they were caring for a group of diabetic patients at sea level rather than fit athletes living a robust outdoor life. Whether the chronic hypoxic state depresses the immune response, or whether the problem is hypoxic interference with wound healing combined with marginal personal hygiene—or some other factor altogether—is a question to be answered in the future.

The most intriguing medical problems we faced were the various manifestations of acute mountain sickness. This term encompasses a variety of symptoms that occur when sea level residents ascend to

higher elevation. Mild symptoms include headache, lethargy, insomnia and anorexia. If a person so afflicted does not rest or descend to a lower altitude, these symptoms can progress to shortness of breath, painful and nonproductive cough, peripheral edema, cyanosis, nausea, weakness and a mental state of indifference. In its most severe form, acute mountain sickness progresses to pulmonary and cerebral edema, unconsciousness, severe arterial blood desaturation and death.[4]

This potentially lethal syndrome is not the inevitable result of going to a high altitude; it can usually be avoided by a gradual ascent. The maxim is, ascend slowly, and if you feel poorly or become ill, descend quickly. AMREE was careful to ascend at a rate comfortable for all its members, and we avoided most of the problems of acute mountain sickness. Despite our care, however, high-altitude pulmonary edema (HAPE) developed in two members and one visitor.

The variable presentation of high-altitude pulmonary edema was impressively seen during our expedition. The visitor to the expedition, 25 years of age, felt unwell on his initial ascent to high altitude. He descended and reascended to base camp (5,400 m) and spent nine days there, feeling reasonably well. On his tenth night at this altitude he awoke in the middle of the night severely short of breath, coughing and with rales throughout both lung fields. Fortunately he was sharing a tent with a chest physician, who quickly diagnosed high-altitude pulmonary edema, made the patient comfortable sitting up and administered oxygen by face mask. By morning, the ill visitor was able to walk with assistance and descended to lower altitude where he made an uneventful recovery.

In one of the expedition's most powerful athletes, mild high-altitude pulmonary edema developed after strenuous climbing with a heavy backpack to Camp III (7,250 m). The pulmonary edema cleared rapidly with descent and he later reascended to 8,000 m, using supplementary oxygen via mask, and spent several nights at 7,500 m without difficulty. After a rest at lower altitude he again climbed high on the mountain, but this time he ascended to Camp IV (7,500 m) with a sizable pack and no supplementary oxygen. He became ill and returned to Camp II complaining of severe postural dyspnea, which he characterized as "a feeling of drowning in tracheal secretions [he is a physician] whenever I lie down." It was notable that when he was accompanied down the glacier, he was able to make good speed during the descent, but that even the smallest uphill section of terrain was a terrible strain and he became visibly cyanotic with the effort. When he arrived at base camp his blood hemoglobin-oxygen saturation was measured and found to be 70%. Although this was low, the more striking finding was a profound drop to 50% saturation with very mild exercise. This climber again recovered quickly at base camp.

The other case of high-altitude pulmonary edema occurred in an expedition member who was asthmatic and had considerable difficulty with his airway disease during the climb. Nevertheless, he ascended to 7,400 m and played a major role in establishing the camps at 6,800 m and 7,400 m. On his return from the upper camps he had a combination of bronchitis, asthma and chest congestion. With the resolution of his first two problems with antibiotics and rest, it was apparent he had a significant component of pulmonary edema that cleared only after descent to base camp and oxygen administration for two days. We saw no evidence of cerebral edema in any of our members.

Severe peripheral cold injury (frostbite) has been a major cause of morbidity during previous attempts to climb Mount Everest. Our group suffered no frostbite, and we feel that the attention to the personal health measures mentioned earlier and our excellent insulating clothing and boots protected us. Although much of our gear was the current version of traditional designs and materials, the use of three recently developed materials is worth noting. All the high-altitude climbers wore windproof suits made of a Teflon-nylon laminate. The expanded Teflon membrane that is bonded to the nylon (Gore-Tex, WL Gore & Associates, Inc, Elkton, Md) is familiar to the medical profession because it is used to make vascular grafts. When bonded to fabric, the membrane makes a material that is totally windproof without being excessively heavy or impermeable to water vapor generated by the body. Gore-Tex was also used as a covering in our sleeping bags, which were filled with goose down.

Our boots, made in Austria, were fashioned of a nylonlike material that was durable and extremely lightweight. Although this material does not have exceptional insulating properties, it never becomes wet or frozen, and its rigidity protects the feet from pressure caused by straps used to secure crampons (the steel spikes used for climbing up ice). These boots were comfortable and entirely satisfactory.

Insulating clothing fashioned of a furlike synthetic pile fabric was widely used. This pile fabric is soft, nonirritating, light in weight and warm. It does not absorb moisture and thus retains its insulating properties when wet, and it dries quickly. It largely replaced wool on our expedition as the preferred fabric for underwear, sweaters and trousers.

Our diet was based on locally available fresh food. Marvelous potatoes and winter vegetables are grown only a few days' walk from base camp and are available in the autumn. Rice and lentils, as well as occasional fruits, were also available. We perhaps set a world's altitude record by sprouting several kinds of

seeds and beans at our 6,400-m Camp II. The fresh sprouts were always a welcome addition to meals. We supplemented the locally available foods with a large, varied selection of preserved foods brought from the United States, including canned ham, tuna, crab meat and salmon, breakfast cereals, candy, cookies, dried fruits and meats. We used very little freeze-dried food, as previous experiences had convinced us that food preserved in this manner was unsatisfying and often tasteless at high altitude.

Little alcohol was included in our rations, and this scarcity seemed to work no hardship on any member of the group. In the lowlands, moderate amounts of the excellent Nepalese beer were consumed when it was available. A variety of food supplements and vitamins were used by individual members of the expedition, without any obvious advantage or drawbacks.

Conclusion

The head lama at the Buddhist monastery of Thangboche, where climbing expeditions always stop for a blessing on the way to the mountain, gave us the secret of a successful Mount Everest venture: "Luck, harmony and prayer," he told us, in that order. Our team had exceptional luck, wonderful harmony and the lama's prayers. Careful preventive and therapeutic medicine solved the few problems that these three elements did not cover and allowed us all to return home intact.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Thrombolytic Therapy for Pulmonary Embolism

QUESTION:

Should thrombolytic therapy be used for all patients with pulmonary embolism? What are the indications for primary therapy?

OPINION:

In the opinion of the Scientific Advisory Panels on Chest Diseases, General Surgery, Internal Medicine, Nuclear Medicine and Radiology, thrombolytic therapy for pulmonary embolism can be considered established medical practice for selected patients only. There is no evidence to support its use as routine or primary therapy for all patients.

Because of the increased risk of bleeding complications as compared with the use of heparin, thrombolytic therapy is indicated only for documented, massive, life-threatening pulmonary embolisms, particularly those associated with hemodynamic instability and documented deep vein thrombosis.

Thrombolytic therapy for the above is contraindicated when there is increased risk of severe bleeding complications (specifically, active internal bleeding) and any cerebrovascular disease or procedure within the preceding two months. Other more relative contraindications include a recent operation (within the last ten days), organ biopsy, puncture of a vessel that cannot be compressed, recent serious internal trauma, uncontrolled coagulation defects, pregnancy, postpartum period (ten days), cardiopulmonary resuscitation with rib fracture, thoracentesis, paracentesis and lumbar puncture.

The role of thrombolytic therapy for lesser degrees of embolism remains the subject of ongoing investigation and awaits confirmation of long-term benefits.

Medical Progress

Noninvasive Assessment of Carotid Artery Disease

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Noninvasive methods of detecting carotid disease were developed to avoid the morbidity and occasional mortality associated with cerebral angiography. The tests developed are of the following two types: direct, which uses imaging or the detection of flow disturbances to identify disease at the bifurcation, and indirect, which infers the presence of bifurcation disease by detecting changes at a remote site. The initial goal of only detecting disease has now been broadened, with this technology being used to address important clinical and epidemiologic questions such as the natural history of carotid bifurcation disease. The recognition of these important contributions has been compounded, however, by the large number of tests that are available, producing the problem of deciding which test or tests should be used for a particular patient. The use of multiple tests avoids the deficiencies of single tests but compounds medical costs. For a cost-effective single form of testing for all circumstances, duplex scanning methods offer the greatest possibility of detecting all degrees of disease.

In a national cooperative study conducted more than two decades ago, the prevalence of hemodynamically significant arterial lesions in the extracranial carotid artery was documented and the possible role of disease in this location being responsible for symptoms of cerebral and retinal ischemia was emphasized.[1] At that time, cerebral arteriography was the only investigative modality available for identifying disease in the cervical arteries but the morbidity and occasional mortality associated with this procedure[1] necessitated that its use be restricted to the evaluation of patients with symptoms of cerebral ischemia and, as such, restricted its use for investigation in individual patients in whom no clinical signs suggestive of carotid artery disease were present. This limitation also prevented its use in larger studies designed to address the natural history of carotid bifurcation disease. Because of these factors, there was a need for the development of diagnostic methods that could accurately identify disease in the cervical portion of the internal carotid artery with little or no morbidity so that important clinical and epidemiologic questions could be safely addressed. These needs have resulted, in the past decade, in the development and use of a wide variety of noninvasive methods specifically designed to detect disease in this location. The purpose of this article is to review the methods involved in doing these tests and to discuss the relative merits and use of these different methods in clinical practice.

Theoretical Considerations—The 'Ideal' Test

The ideal diagnostic test should satisfy several different requirements, with perhaps the most important being a high specificity or ability to clearly differentiate between normal and abnormal vessels, thus avoiding exposing patients with no disease to further potentially morbid investigative procedures. Given that a test can perform this important discriminant function, one must then ask, what other factors referable to the disease are important to recognize. This question arises because it has become apparent that the mere presence of atherosclerotic disease at the carotid bifurcation does not necessarily identify a patient who is at risk of subsequent ischemic stroke in the area of supply of the affected carotid artery.[2] The initial characteristic thought to predispose to ischemic stroke was the degree of stenosis produced by the lesions, so that patients with disease that produced severe reductions in the luminal diameter were considered to be at the greatest risk of subsequent

Refer to: Bandyk DF, Thiele BL: Noninvasive assessment of carotid artery disease (Medical Progress). West J Med 1983 Oct; 139:486-501.

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cerebral ischemic events.[3] The pathogenesis of stroke in this setting was presumed to be due to an overall reduction in cerebral perfusion, precipitated finally by internal carotid thrombosis. If such were the case, a test capable of identifying such pressure- or flow-reducing lesions would be all that would be required to identify a high risk patient.

Evidence against this uniform concept of pathogenesis of cerebral ischemia has come from several observations. It has been recognized for some time that internal carotid artery occlusion can occur in the absence of neurologic symptoms,[4] which suggests that even if pressure and flow are reduced, other factors appear to compensate for this change and to prevent the serious neurologic sequelae that would otherwise result. One mechanism of compensation, as in ischemia in other areas of the vascular system, appears to be the ability of the collateral system in the brain to provide alternate sources of blood supply. The major factor here is the anatomic status of the circle of Willis, which is complete in only 50% of cases studied at routine autopsy.[5] A further complicating factor relates to whether or not these collateral pathways are themselves compromised by the development of disease, which would then significantly reduce the capacity for compensation. The importance of this collateral pathway mechanism in the pathogenesis of cerebral ischemia has been noted in a clinical study of patients who had transient ischemic events and a second group of patients who had mild, fixed neurologic deficits.[6] In these two different population groups, there was no difference in the severity of disease at the appropriate carotid bifurcation, but a highly significant difference was observed when the presence of siphon disease, or absence of a complete circle of Willis, was compared. Abnormalities in the intracranial portion of the cerebral circulation occurred in about 90% of those patients in whom fixed neurologic deficits developed and only 25% of those who had transient ischemic events. In light of this factor, it would therefore be useful to have a test that could determine the state of the collateral pathway mechanism.

A major advance in our understanding of the role of carotid bifurcation atherosclerosis in causing cerebral ischemia came with the recognition that embolization from these strategically located lesions was a common event that initiated cerebral ischemia.[7] Direct evidence to support this view has come from a detailed examination of plaques removed at operation in patients with transient ischemic symptoms in which gross degrees of surface irregularity and intramural hemorrhage in the substance of the plaque were identified.[8,9] These changes in plaque morphology predispose to rupture of the plaque, with discharge of debris into the lumen of the internal carotid artery flow stream. The presence of the irregular surface could theoretically, at least in association with exposure of subendothelial collagen layers, be capable of initiating local aggregation of platelets and fibrin, which would also subsequently be prone to downstream embolization. The ideal testing method would therefore be able to identify both the surface characteristics and structural details of lesions visualized.

Further consideration of the role of lesion morphology in the pathogenesis of ischemic stroke raises the question of whether there is a relationship between severe stenosis and the morphologic changes that predispose to embolization. Clearly, if this latter series of complications occurs only in lesions that also produce pressure and flow changes, a test that could identify these latter changes would, potentially at least, indirectly identify a high risk patient. A study of the morphology of lesions at the carotid bifurcation in patients with cerebral ischemic events using cerebral arteriography as a method of determining both degrees of stenosis and surface irregularity showed that this latter feature occurred with almost equal frequency in lesions producing less than 50% diameter reduction (45% versus 55%). Clearly then the surface characteristics of lesions need to be identified independent of the ability of a test to detect stenosis.

In summary, the goals of any form of testing should be to clearly differentiate between vessels that are normal and those that are diseased; to identify disease regardless of the magnitude of diameter reduction and be capable of differentiating between flow-reducing and non-flow-reducing lesions; to identify the presence of lesion surface irregularity of varying degrees; to identify the structural features of a plaque, particularly the presence of hemorrhage, and to assess the ability of the complex collateral pathways to compensate for the presence of flow-reducing lesions in the internal carotid artery. Given all these pathophysiologic considerations regarding the ideal form of testing, the last requirement is that the method or methods used must be cost-effective so that screening of large populations at risk may be done. With these factors clearly defined, one is able to realistically assess the role of various methods of diagnosis of extracranial carotid artery disease that are available.

General Principles of Testing

The tests that have been developed specifically to detect carotid artery disease are of two different types—direct and indirect (Table 1). The direct tests scrutinize the area of the carotid bifurcation to identify disease at this location, using either imaging techniques or physiologic methods of detecting flow disturbances generated by the presence of disease (or both). In contrast, the indirect tests use physiologic variables as the sole means of identifying disease, detecting changes at a site remote from the bifurcation, usually in the ocular globe or the periorbital circulation itself.

Indirect Tests

Supraorbital Doppler. The periorbital Doppler examination is a physiologic test that uses a direction-sensing Doppler system to evaluate flow direction in the medial frontal or supraorbital arteries.[10] Under normal conditions, blood in the supraorbital and frontal arteries

TABLE 1.—*Classification of Noninvasive Cerebrovascular Tests*

	Physiologic Method	*Imaging Technique*
Direct Tests . . .	Carotid phonoangiography	Ultrasonic B-mode imaging
	Qualitative	
	Quantitative	Ultrasonic flow imaging
	Doppler sound analysis	
	Continuous wave (analog, spectral display)	
	Pulsed (spectral display)	
Indirect Tests . .	Supraorbital Doppler	
	Oculoplethysmography	
	Pulse-delay	
	Pressure	

flows out of the orbit to supply the skin above the eye. When a stenotic lesion of the internal carotid artery produces a pressure gradient of sufficient severity, flow in these arteries will reverse and become retrograde into the orbit. A Doppler probe positioned over the supraorbital or frontal arteries in combination with a series of compression maneuvers is used to evaluate the magnitude and direction of flow. Flow is normally towards the probe and will increase when the superficial temporal, infraorbital or facial arteries are compressed. When the internal carotid artery is severely narrowed or occluded, flow to the retina will be from the orbital branches of the external carotid artery and away from the probe. The amplitude of the signal will diminish, cease or reverse when one or more branches of the external carotid artery are compressed. Because of the complexity of available collateral pathways, compression of contralateral external carotid branches, or ipsilateral and contralateral common carotid arteries may be required to determine the source of the periorbital blood flow to establish a diagnosis of hemodynamically significant extracranial carotid artery occlusive disease.[11] The results of this test are depicted as an analog waveform on a strip chart recorder enabling easy interpretation of flow direction and signal amplitude. The type of lesions that theoretically are capable of detection with this form of testing are those that produce reductions in pressure or flow only.

Oculoplethysmographic methods. The principle common to all of these methods is the use of the eye as a means of identifying changes in pulse wave arrival, pulse wave amplitude or absolute ocular pressure to detect lesions in the ipsilateral internal carotid capable of producing these changes. In general, this represents lesions that produce 75% or greater area reduction of the lumen of the internal carotid artery. The rationale for using the eye originates in the anatomic relationship of the ophthalmic artery as the first branch of the internal carotid artery, and changes in physiologic measurements produced by internal carotid disease will be mirrored by changes in the ocular bed. The various types of oculoplethysmography are often confused, and because each test measures a different physiologic variable relative to ophthalmic blood flow, they should be discussed separately.

Pulse delay oculoplethysmography (Kartchner & McCrae). This method of testing uses plastic corneal cups filled with water applied to the sclera with a negative pressure of 40 to 50 mm of mercury. A pulse wave representing the volume change in the eye with each heart cycle is detected from each eye. Pulse wave arrival time and configuration are compared between each eye and referenced to an external carotid artery pulse wave recorded from each earlobe using photoplethysmographic clips. The results are recorded in analog format, recording the eye volume tracings together with a differential recording to facilitate detection of minor differences in both amplitude and timing between the two eyes. Finally, a recording from the earlobe is displayed for comparison with the ocular tracings. A long collateral artery pathway and changes in arterial compliance due to the presence of proximal hemodynamically significant internal carotid artery stenosis result in a delay in pulse wave arrival or distortion of the ipsilateral ocular pulse most readily apparent on the differential tracing, or both. Bilateral internal carotid artery occlusive disease is detected by comparing the timing characteristics of the ocular and ear pulse waveforms. Results of the test are reported in semiquantitative fashion by determining the magnitude of the difference in pulse wave arrivals. The categories of disease supposedly capable of detection with this technique are (1) less than 40% diameter reduction, (2) 40% to 60% diameter reduction, (3) 60% to 70% diameter reduction, (4) 70% to 85% diameter reduction and (5) greater than 85%. Whereas this method initially was enthusiastically adopted by both clinicians and researchers,[12] considerable controversy regarding its accuracy subsequently became apparent.[13,14] Whereas an abnormal test result obtained with this method gives a high index of suspicion of the presence of disease, the overall sensitivity and specificity of the test are inadequate for routine diagnostic use.

Pressure plethysmography. Pressure oculoplethysmography developed by Gee and co-workers[15] simultaneously measures the systolic arterial pressure in the ophthalmic arteries. Suction cups applied lateral to the cornea are held in place with a negative pressure (300 to 500 mm of mercury) and used as a means of increasing the intraocular pressure. Arterial pulsations from the eye are detected by the same scleral cup. When intraocular pressure exceeds ophthalmic artery pressure, pulsatile flow ceases while reduction of the intraocular pressure allows determination of systolic pressure by recording when the onset of pulsation occurs. A significant internal carotid lesion is diagnosed using the following criteria: the intraocular pressure at the point of ocular pulse return is less than 66% of the brachial artery pressure, or the pressure in one eye exceeds that in the other by 5 mm of mercury. Pressure oculoplethysmography is an accurate method of detecting high-grade carotid artery stenosis and occlusion when compared with arteriography. Perhaps the most important feature of this method is the ability to determine the adequacy of functioning intracranial and extracranial collateral

pathways when it is combined with common carotid artery compression. The adequacy of collateral pathways assures that obliteration of the carotid lumen will not produce global cerebral ischemia. This diagnostic capability has been useful for physicians in deciding whether or not carotid ligation is safe in cases of carotid artery trauma, and in managing patients with surgically inaccessible intracranial aneurysms.[16,17] It has also been used in the selection of patients for an extracranial-intracranial artery bypass procedure.[18]

Of the plethysmographic methods currently available, that developed by Gee appears to be the most useful technique. While it is potentially only capable of identifying relatively high-grade lesions, the attractiveness of this test lies in its ability to accurately quantify the capacity of the collateral circulation to compensate for internal carotid artery occlusion. A major criticism of these tests initially was an inability to differentiate between high-grade stenoses and internal carotid artery occlusion, but this deficiency has virtually disappeared with the development of the superficial temporal middle cerebral artery bypass procedures that provide a therapeutic alternative for patients with internal carotid artery occlusions. Before the development of this treatment modality, arteriography in such patients was an unnecessary investigation.

Direct Tests

The direct methods of testing obtain information from the extracranial segment of the carotid artery in the vicinity of the carotid bifurcation. The value of these direct tests relies on the association between disease at the bifurcation and cerebrovascular insufficiency. The direct physiologic tests currently available include carotid phonoangiography (qualitative and quantitative), continuous wave Doppler scanning and Doppler sound spectral analysis (continuous wave or pulsed). Most of these methods use advanced techniques of frequency analysis of sound originating or reflected back from the flow stream at the bifurcation.

Qualitative carotid phonoangiography. This technique uses the principle of amplifying bruits in the region of the neck with a concrete display of the form and timing of the bruit. A hand-held microphone is placed over the carotid artery in the low, middle and high locations.[19] Bruits may originate from the internal carotid artery when the diameter is reduced by only 30%, but are more likely to be present when the stenosis exceeds 50% diameter reduction. As the severity of the stenosis increases, bruit intensity diminishes greatly and finally disappears when the vessel is completely occluded. The bruit itself is generated by disturbances in the flow stream that are then transmitted to the vessel wall, which vibrates at varying frequencies, depending on the magnitude of the disturbance. The bruit, supposedly classical for the presence of internal carotid disease, is one that originates in the midcervical region of the neck and is transmitted to the high position immediately inferior to the earlobe. A pathologic bruit also usually lasts into diastole. While this technique may be used by itself to detect carotid artery disease, its most frequent application has been as an adjunct to oculoplethysmography in an effort to increase the sensitivity of this test. In this setting, concordant results have been shown to increase both the sensitivity and the specificity of the method.[20] An obvious major deficiency of the method, however, is the fact that disease itself does not uniformly produce bruits and whereas bruit intensity is related to the magnitude of the flow disturbance within the lumen, vessel wall characteristics are also an important factor that may explain some of the problems with the use of the method.

Quantitative phonoangiography. This technique uses spectral analysis of the frequency content of an arterial bruit as a means of estimating residual lumen diameter. It has been shown that the residual lumen diameter in the region of an atherosclerotic plaque can be estimated by mathematical analysis of sounds produced within the vessel.[21] Certain assumptions regarding peak systolic flow velocity are made and calculation of the residual lumen diameter depends on the recording of the "break frequency" of the bruit. The "break frequency" is a characteristic of the sound produced by turbulent flow. A microprocessor is used to analyze the audio-frequency data and the residual lumen diameter of the internal carotid artery is calculated. The residual lumen diameter calculated by this technique agreed with angiographic measurements to within 1 mm in 85% of bruits that could be analyzed.[22] Clinical application of this method is limited by the same limitation of qualitative phonoangiography in that about 40% to 60% of patients in whom hemodynamically significant stenoses have been angiographically documented will have no bruits present. When a bruit is present, however, quantitative phonoangiography can provide an accurate estimate of residual lumen and is therefore of value in determining progression of disease in asymptomatic patients with a bruit.

Continuous wave Doppler scans. This technique uses the principle that with a flow- or pressure-reducing stenosis, the velocity of erythrocytes immediately distal to the area of the stenosis increases as attempts to maintain the flow rate occur. Insonation of the flow stream with continuous wave ultrasound will result in a backscatter of the signal with a frequency shift proportional to the velocity of the erythrocytes.[23] In this technique, a continuous wave probe inclined at an angle of about 60 degrees is traversed along the internal carotid artery, the bulb of the internal carotid artery and the common carotid, while a continuous recording of the peak frequency of the backscattered signal is done on a strip chart recorder. Audible interpretation of the Doppler signals is also possible by a trained observer, as the ear is extremely sensitive to the changes in frequency that occur in the presence of high-grade lesions.[24] The test is positive when, during scanning along the line of the carotid vessels, the peak frequency is shown to increase (Figure 1). In the hands of experienced observers, this relatively simple method has been shown to be capable of correctly identifying 90% of cases of severe (more

than 50% diameter reduction) stenosis or occlusion when audible interpretation of the signal is used. It should be emphasized that the technique requires considerable examiner knowledge in both the principles of ultrasonic physics and the anatomy and pathology of the carotid bifurcation. This technique is more accurate than indirect physiologic testing methods in identifying a hemodynamically significant stenosis and, perhaps more important, total occlusion can be differentiated with some degree of accuracy.[20] The major deficiency of this method of testing relates to the difficulties encountered due to changes in the angle of the incident Doppler beam, minor variations in which may be responsible for the production of a false-positive test (Figure 2). In addition, anatomic variation in the location of the carotid vessels, a feature occurring in about 10% of patients, may be responsible for considerable confusion in interpretation of the results by an examiner, contributing to both false-positive and false-negative studies.

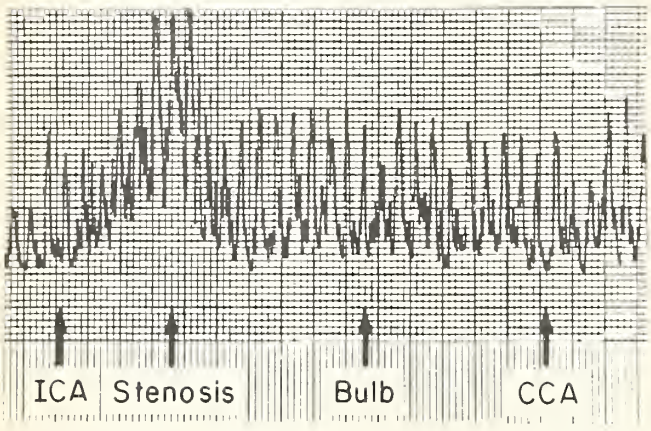

Figure 1.—Continuous wave Doppler scan of the carotid bifurcation. An analog recording shows the increase in frequency across the area of the stenosis signifying an increase in erythrocyte velocity across this region. ICA = internal carotid artery, CCA = common carotid artery.

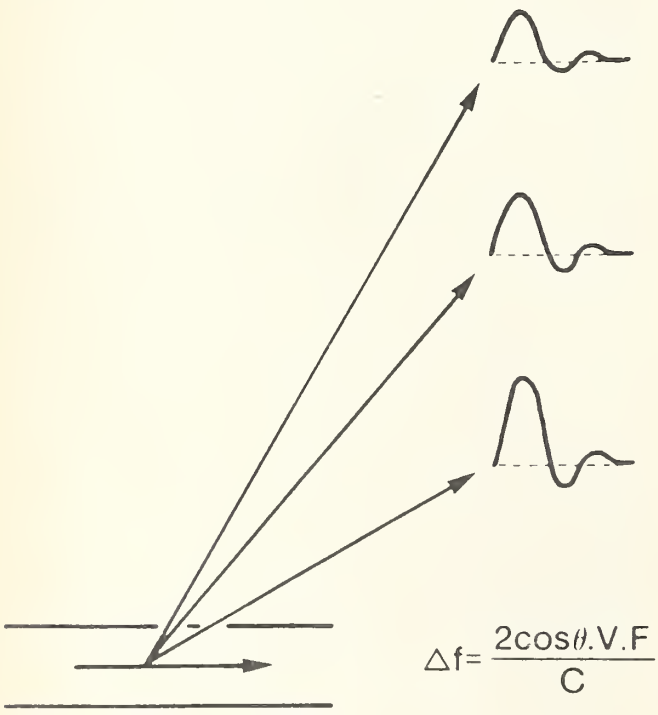

Figure 2.—Effect of the Doppler angle on the dimensions of the analog signal. This diagram shows how an acute angle may produce false high frequencies and a steep angle may artificially dampen high frequencies. Doppler equation is shown with relationship between frequency (f) and incident angle of Doppler beam (θ) (Δf = frequency shift, V. = velocity, F. = transmitting frequency).

Quantitative continuous wave methods. The difficulties that are produced by artifactual variations in peak frequency due to variations in the angle between the probe and longitudinal axis of the carotid vessels can be overcome by "normalizing" the results. In this method, a number of easily identifiable points in the velocity waveform of the common carotid artery are expressed as a ratio, which is thus angle independent. The simplest form of this approach was reported by Plainiol and Pourcelot,[25] who used a resistance index derived from the common carotid waveform. They observed that when this ratio was greater than 0.75, high-grade stenosis of the internal carotid artery was likely. This observation depends on the unique physiologic characteristics of the common carotid artery flow pattern that in nondiseased states mirrors the velocity waveform characteristic of the internal carotid artery. When this latter vessel is occluded, the common carotid waveform resembles that of external carotid artery. Because the cerebral circulation is a low-resistance vascular bed, flow in diastole is in the forward direction and at no point in the pulse cycle does it approach zero. Because the external carotid artery supplies a high-resistance bed, flow not only reaches zero but actually reverses during diastole. Thus when flow in the common carotid artery is seen to approach zero, occlusion of the internal carotid artery is likely. False-negative results occur with this method, in circumstances in which the external carotid artery is a major collateral for the cerebral circulation, when the waveform characteristics of this vessel may resemble those of a normal internal carotid artery and produce little change in the common carotid waveform. False-positive results are uncommon with this method. Difficulties with this method are experienced due to beat-to-beat variations of peak systolic frequency and unsatisfactory waveforms due to "noise" in the system. The clinical usefulness of this relatively simple approach was documented by Archie,[26] who showed it was capable of identifying 91% of hemodynamically significant lesions of the internal carotid artery. The specificity of the method is low and prevents its widespread use.

Reinertson and Barnes have used multiple ratios from the common carotid to identify varying degrees of stenosis and have shown in an experimental model that even relatively minor degrees of diameter reduction

produce changes in the velocity waveform proximal to the stenosis.[27] In spite of these findings, the method has not been widely adopted because the computations have to be done manually off line and are therefore time consuming. In spite of this limitation, these workers have shown that quantitative analysis of data derived from relatively simple instrumentation is capable of accurate identification of a wide range of lesions (95% accuracy).[25] These relatively cheap and simple methods of testing have been replaced by more sophisticated techniques not necessarily because the potential capabilities of the former have been exhausted, but rather because the latter were readily available from other ultrasound disciplines.

Imaging Systems

Contrast arteriography is the accepted "gold standard" imaging method for the diagnosis of cerebrovascular occlusive disease. The time, expense, patient discomfort and risk associated with this technique, however, limit its use as a screening or patient follow-up diagnostic procedure. Noninvasive imaging systems are appealing because of the potential ability to detect nonstenotic lesions and provide a morphologic image similar to that obtained with conventional arteriography.

Ultrasonic imaging. Images of the carotid bifurcation are generated using ultrasound for the detection of either flow in the vessel (ultrasonic arteriography) or by identifying the blood-arterial wall interface due to the different acoustic impedance of the two structures (B-mode ultrasound imaging). Ultrasonic methods are ideally suited for the investigation of extracranial carotid artery disease for the following reasons: Atherosclerotic stenosis and ulceration are usually localized to the carotid bulb and the first few centimeters of the internal carotid artery, the carotid bifurcation is superficially located and accessible to ultrasound penetration and diagnostic ultrasound consists of nonionizing radiation and has no known harmful effect on patients.

Ultrasonic flow imaging. Ultrasonic flow imaging was initially used to generate flow images of the carotid bifurcation from which the degree of vessel narrowing could then be estimated.[28] The resulting flow maps resemble conventional roentgenograms (Figure 3),

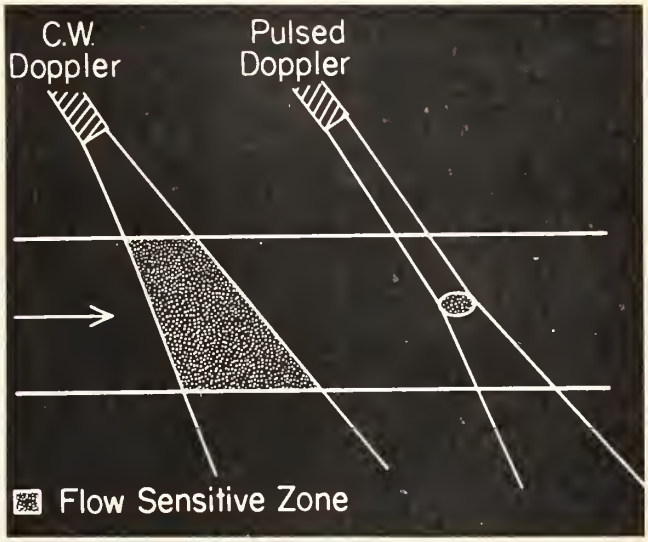

Figure 4.—Diagrammatic representation of the difference in volume of the flow stream evaluated by continuous wave (C.W.) and pulsed Doppler systems.

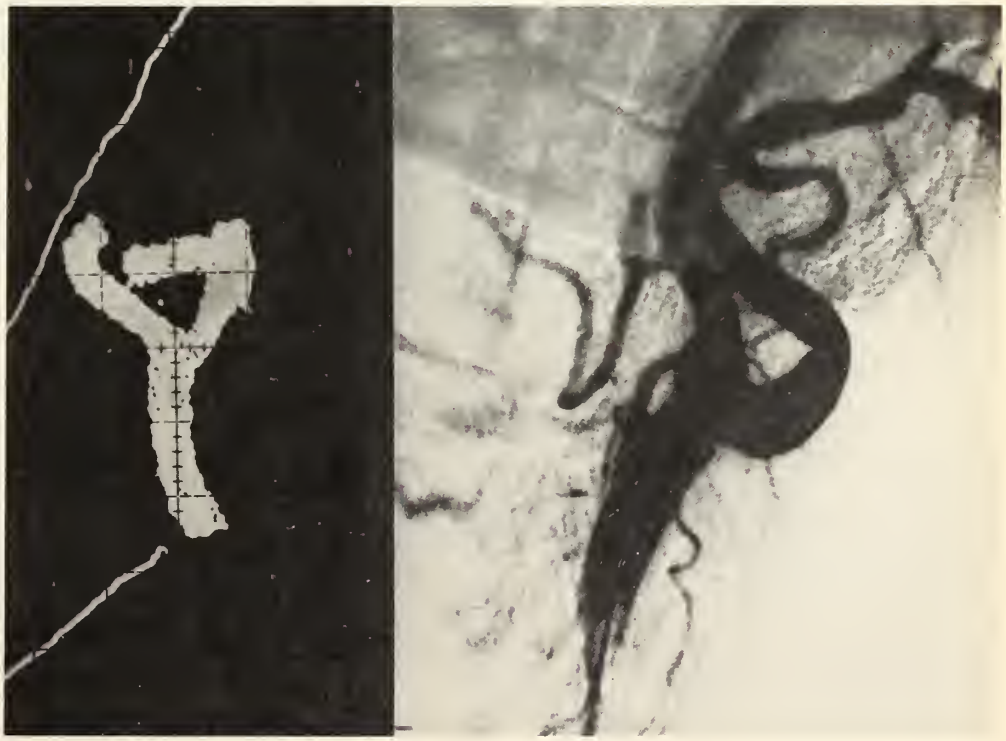

Figure 3.—Ultrasonic arteriogram (**left**)) and conventional arteriogram (**right**) of a normal carotid artery bifurcation. These pictures show the similarity between the two.

which, with the aid of a small computer, can also provide simultaneous longitudinal and transverse images in multiple planes.[29] The Doppler devices used in this manner are of two different types—one with a pulsed Doppler source and one with a continuous wave Doppler source.[30,31] A pulsed Doppler system emits short bursts or pulses of ultrasound and, depending on the transmitting frequency, pulse repetition frequency, and focusing technology, can insonate a finite volume of tissue or fluid (Figure 4). This technology is ideally suited for the study of flow in vessels because it can sample discrete points in the flow stream. If multiple gates are used, information from multiple locations in the cross-sectional flow stream may be obtained either simultaneously or sequentially. The continuous wave systems insonate the entire cross section of the vessel and shifts in the backscattered frequency are representative of variations in the velocity of all the erythrocytes in the path of the sound beam across the entire vessel. With the former technique, the limits of the vessel wall are identified as the points at which no significant Doppler shift is detected and this "no flow" zone is recognized electronically. Only significant Doppler shifts activate the imaging system, which allows gradual compilation of a "flow image." The continuous wave systems are not true imaging systems in the sense that they define the margins of the vessel being examined, but rather identify changes in the frequency of the backscattered Doppler signal as a method of detecting stenoses that produce such changes.[30,31] The resulting flow image is actually representative of mean blood cell velocity at varying locations in the vessel, with interpretation facilitated by using a color-coded display. Although they are usually referred to as methods of ultrasonic arteriography, they are, in essence, physiologic flow interpretation systems.

In general terms, the best results have been obtained using a multigated pulsed Doppler system. This technique allows an estimate of the stenosis to be made with recognition of 90% of the severe lesions (greater than

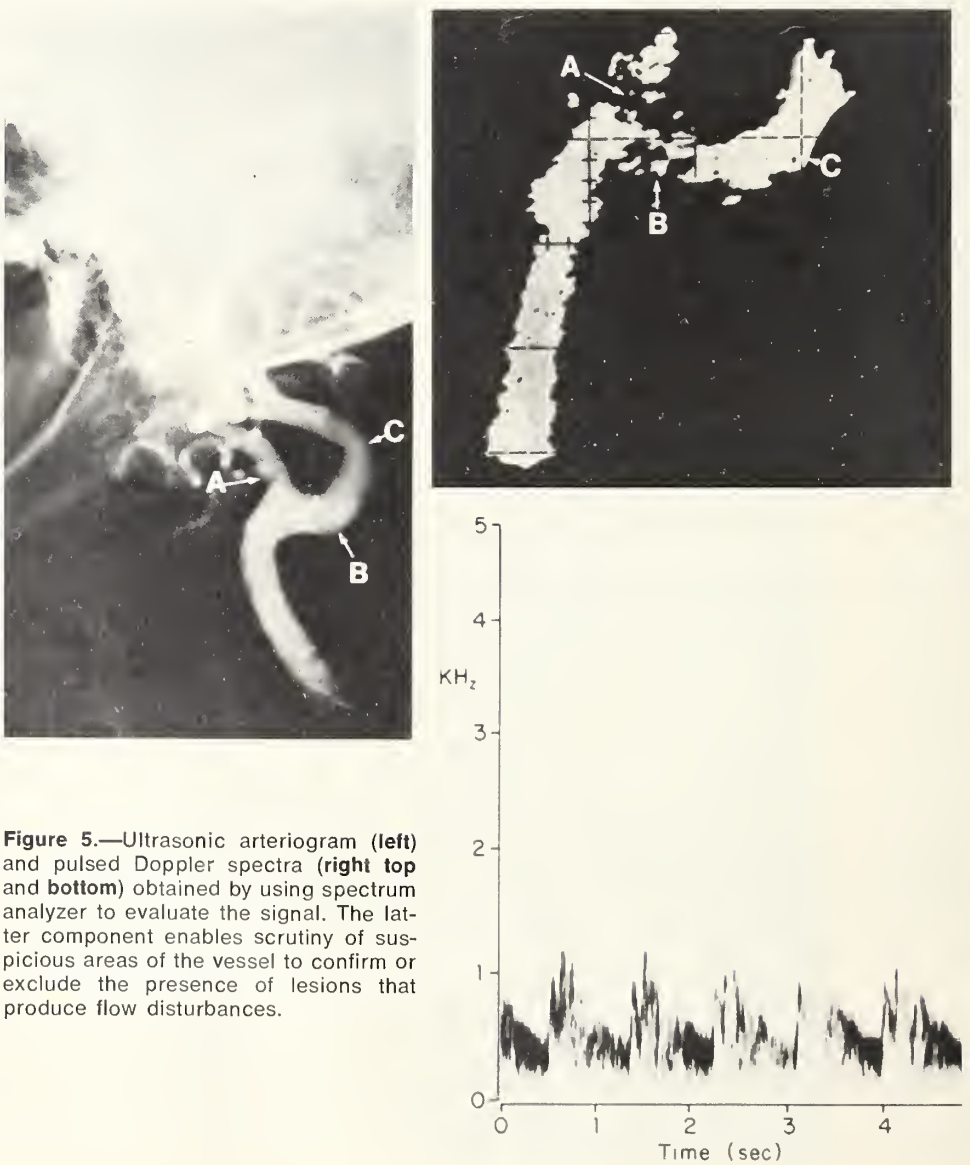

Figure 5.—Ultrasonic arteriogram (**left**) and pulsed Doppler spectra (**right top** and **bottom**) obtained by using spectrum analyzer to evaluate the signal. The latter component enables scrutiny of suspicious areas of the vessel to confirm or exclude the presence of lesions that produce flow disturbances.

50% stenosis). Whereas this testing method was extremely accurate for identification of high-grade lesions, the specificity was relatively low and cases of occlusion and stenosis with less than 50% diameter reduction could not be recognized with acceptable accuracy.[28] Ultrasonic flow imaging is hindered by the presence of calcium in the arterial wall, which interferes with the transmission of ultrasound, thus distorting the flow images and rendering them uninterpretable in about 10% of examinations. The non-axisymmetric nature of atherosclerotic plaques also reduces the specificity or sensitivity of the test due to projection error unless multiple cross-sectional images are obtained, a feature possible with the addition of computer technology. Another major problem in diagnosis can occur in patients in whom rotational variations in the anatomy of the carotid bifurcation are present, making it difficult to identify which vessel is the internal carotid artery. The examination requires about 20 to 30 minutes to do, and because the images are sequentially built up by moving the transducer over the bifurcation, patient movement results in a loss of the preexamination baseline XY coordinates, in which case the test must be repeated. Uncooperative patients are therefore not suitable for study with this method. The accuracy and usefulness of this technique have been significantly improved by coupling the system with a spectrum analyzer and using changes in characteristics of the spectra as the primary method of diagnosis, rather than the pure flow image (Figure 5). This latter modification overcomes most of the problems encountered with the initial instrumentation.

Ultrasonic B-mode imaging. Pure B-mode ultrasonic imaging is a diagnostic method used extensively in medicine that has been applied successfully in a wide variety of disciplines. Application to the evaluation of carotid bifurcation disease has been more recent and is at an early stage of development. Real-time B-mode imaging can visualize the carotid bifurcation and detect plaques at various stages of progression.[32] The clinical application of this technique is limited by many of the factors that create problems for the ultrasonic flow imaging systems. Variations in anatomy of the carotid bifurcation can be difficult to interpret, but perhaps the major difficulty is generated by the heterogeneous structure of atherosclerotic plaques at different stages of development because the acoustic properties may vary. Calcium, in particular, is a common component and serves as a barrier to high resolution of the surface margins of a plaque.[33] An additional major difficulty is that flowing blood has a similar density to blood clot. Because hemorrhage is a frequent complication of atherosclerotic plaques in this location, these areas will appear as large acoustic shadows, the extent of which may be very difficult to interpret. When the structure of atherosclerotic plaques is homogeneous, as is usually the case in relatively early phases of development, the high-resolution systems are capable of accurately identifying these lesions. Studies conducted to date comparing the accuracy of this examination with contrast arteriography have confirmed that the technique is useful for identifying relatively minor lesions but the sensitivity for detecting more severe degrees of stenosis with complex atherosclerotic plaque structure is not good enough for routine clinical use.[34] Whereas it was hoped that these systems would be capable of identifying ulceration with a high degree of accuracy, one of the major disappointments has been the consistent inability to identify ulceration or irregularity when present. It has become obvious that the current imaging systems in and of themselves are not accurate enough for routine diagnostic use but have served more as a road map to measure flow in the areas being insonated.

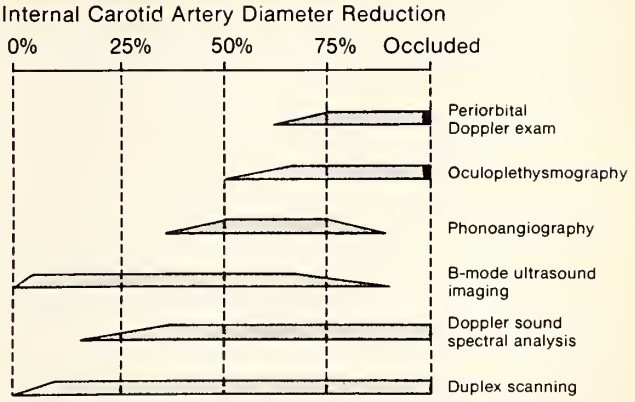

Figure 6.—Schematic representation of the diagnostic range of noninvasive cerebrovascular tests. Optimal results should be obtained with combined testing if there is overlap of the range of disease identified by each test.

Combined Methods

The detection and classification of the extent of occlusive disease at the carotid bifurcation can be improved by using multiple tests but only when the results of each test agree. The accuracy of combined testing is increased over single testing if each test measures different physiologic or anatomic variables and the sensitivity of each test is maximal over different ranges of severity of occlusive disease (Figure 6).[20] In general, indirect physiologic tests detect only severe occlusive lesions, whereas direct physiologic tests and imaging systems are sensitive to lesser degrees of disease. A widely used test combination is that of pulse-delay oculoplethysmography and carotid phonoangiography, a combination of an indirect and a direct physiologic method.[35,36] When each test gives positive results, the sensitivity and specificity of the cerebrovascular examination are improved compared with each test used alone. Extensive evaluation of these techniques,[13,36] however, and the superior results from other methods have caused the gradual decline in the clinical applicability of oculoplethysmography and carotid phonoangiography.

Duplex systems. The most notable advances have come from using combinations of anatomic and physiologic methods. Duplex scanning combines two direct noninvasive methods, B-mode ultrasound scanning and

pulsed Doppler sound spectral analysis. The duplex concept is based on the ability to define the walls of a vessel with a two-dimensional image and subsequently use a Doppler system to evaluate the blood velocities at discrete points within the artery visualized. Diagnostic information is obtained primarily from changes in the backscattered Doppler flow signal, with increased diagnostic accuracy being provided by spectral analysis of the Doppler velocity patterns distal to atherosclerotic lesions. While the imaging and flow detection systems can be combined when continuous wave ultrasound is used, the most accurate results have occurred when pulsed Doppler systems have been used as the basis for both the imaging and velocity detection components. The complexity of the system requires that the operator be totally familiar with ultrasonic imaging as well as pulsed Doppler technique and principles. The assessment of the extent of disease, based entirely on analysis of the Doppler signal, requires careful attention with regard to the position of the Doppler sample volume within the lumen relative to the location of the lesion. An understanding of the hemodynamic effects of stenosis is essential for subsequent interpretation of the results. Currently, Doppler velocity information distal to the area of the lesion in the internal carotid artery provides the major means of both detection and classification of the severity of disease.

Experimental studies have provided important information regarding both the pattern of flow disturbance that occurs relative to varying degrees of stenosis and also the extent of propagation of these disturbances distal to the stenosis.[37]

In studies using dog thoracic aorta as a model, local reductions in luminal diameter of as little as 15% produced identifiable changes in the Doppler velocity spectrum immediately distal to the area of stenosis.[38] These changes in the spectral pattern, evident as increases in spectral width, are indicative of the development of flow disturbances before the onset of overt turbulence and before the development of a pressure gradient across the stenosis. Not only did the magnitude of the changes in spectral width gradually increase with increasing degrees of stenosis from 15% to 50% diameter reduction, but the time of onset of these changes in spectral width occurred earlier in the pulse cycle. With minor stenosis, the maximum changes in spectral width were seen in diastole, while with more severe stenosis, these changes were first seen at peak systole and persisted throughout the duration of systole and diastole. The application of fast Fourier transform analysis to the processing of Doppler signals has provided the theoretic capability of identifying minor lesions. These observations had also been made in early clinical studies and changes in the magnitude and timing of onset of spectral width changes provide the current methods of diagnosing lesions in the 0% to 50% diameter reducing category.

The development of a pressure- and flow-reducing lesion in the internal carotid is evidenced by the aforementioned changes in spectral width in association with an increase in the peak frequency due to an increased velocity of erythrocytes through the stenosis as an attempt is made to compensate for the reduction in luminal cross-sectional area. Because increases in peak frequency can be artificially produced by unrecognized changes in the angle of the incident Doppler beam relative to the axis of the vessel, an important design feature of this instrument includes control of the angle of the incident Doppler beam if accurate results are to be obtained. With severe stenosis of a magnitude of 80% diameter reduction, pulsatile flow distal to the area of the stenosis disappears and is replaced by a

Figure 7.—Intravenous digital subtraction arteriogram of a carotid bifurcation (**left** and **center**) with resolution similar to an intraarterial subtraction study showing a normal vessel (**right**).

continuous pattern of total flow disruption. The sensitivity of this method for all degrees of stenosis exceeds 90% but specificity is low[39] due to the problems created by the generation of flow disturbances in the region of the bulb in healthy persons. While it was thought that minimal degrees of vessel wall irregularity and ulceration may produce localized flow disturbances that could be identified with sensitive Doppler systems, this has not been possible. Detection of minimal degrees of irregularity or ulceration in the absence of severe stenosis is likely to be achieved only with a high-resolution B-mode system. Thus, the ideal combination of testing methods would appear to be that of high-resolution B-mode and Doppler systems. A persistent limitation of the Doppler system is that the results are interpreted qualitatively from a hard copy sound spectrum obtained during the examination and are therefore likely to be subject to observer interpretation variability. Clearly, the definitive method of testing will involve an online quantitative analysis of the Doppler spectrum with a simple printout of the examination results in terms of percentage of diameter reduction.[40]

Digital subtraction arteriography. Digital subtraction arteriography has recently been introduced for the assessment of peripheral vascular disease, and preliminary results of studies evaluating its accuracy in the detection of extracranial carotid artery disease are promising (Figure 7).[41] While the intravenous method of injecting contrast material, combined with digital subtraction imaging, has been promoted as having less risk than conventional selective intraarterial cerebral arteriography, the intraarterial method has gradually become safer as it has been more extensively used and safer contrast agents have been developed. There is probably very little difference in the morbidity of the two procedures, though the intravenous method has a number of appealing advantages. The method does not require admission to hospital, is less expensive and produces images of the carotid arterial system that correlate well with standard arteriography. Digital subtraction arteriography should be considered an invasive method of carotid artery evaluation due to the requirement of contrast injections and the use of ionizing radiation. Misinterpretation of the images from this technique occurs in the presence of extensive carotid bifurcation calcification and also with soft tissue motion, rendering about 12% of the examinations unsatisfactory.[42] Motion artifact can be reduced by means of computer algorithms that use time-energy subtraction (hybrid) rather than time subtraction techniques only to produce an image. This hybrid technique requires additional x-ray exposure and reduces the resolution of the images. A further problem associated with this examination is that only single plane views of the bifurcation are produced and vessel wall detail may be obscured significantly by overlap (Figure 8).

The intravenous method of digital subtraction arteriography has not been found to be a better "gold stan-

Figure 8.—Intravenous digital subtraction arteriogram (**left**) with poor visualization of the proximal internal carotid artery due to vessel overlay (**arrow**) and standard contrast arteriogram (**right**) of the same bifurcation showing a high grade stenosis.

dard" than intraarterial studies. The technique is limited by interpretation and projection error and, even with technically adequate studies, cannot reliably define lesion morphology.[43] Digital subtraction arteriography is sensitive in detecting hemodynamically significant carotid artery disease, with most false-positive results being produced by lesions in the carotid siphon that are poorly visualized. Whether this method has sufficient resolution to document progression of disease or is appropriate for patient screening remains to be proved.

Noninvasive cerebrovascular testing and digital subtraction arteriography appear to have comparable accuracy in detecting hemodynamically significant carotid artery disease defined as greater than 50% diameter reduction of the internal carotid artery.[44]

The Gold Standard

The development of noninvasive methods of diagnosing extracranial carotid artery disease, with the relatively subjective method of interpretation, has introduced the problem of observer variability in reporting results. Apparently this same problem of observer variability is seen in the reporting of standard contrast arteriograms.[45] Clearly, when one is attempting to determine the sensitivity and specificity of a new testing method, observer variability of the reference standard at the various decision points will preclude meaningful comparisons. A major problem exists in the arteriographic recognition of what constitutes a normal internal carotid artery. In one study, interobserver agreement in defining this category was 57% and intraobserver agreement was 75%.[45] The agreement in arteriographic interpretation of degree of stenosis is more accurate when lesions that produce more than 50% diameter reduction are evaluated. Inconsistencies in the interpretation of contrast arteriography are, for the most part, sufficient to explain the observed disagreement between ultrasonic duplex scanning with spectral analysis and the results obtained with arteriography, particularly in the differentiation of normal and abnormal and lesions of more or less than 50% diameter reduction.

Contrast arteriography has been considered to have a major advantage over the ultrasonic methods with regard to its ability to accurately define lesion morphology, particularly the presence of "ulceration."[46] In comparisons between arteriographic interpretation and operative specimen examination, however, the overall accuracy of arteriography approaches 60% with significant instances of both false-positive and false-negative results for the arteriographic interpretation.[47]

Conclusion

Against this background, one must therefore evaluate each of the methods with regard to both what they are capable of and what is required by the clinical circumstance. Unless this approach is adopted, there is a real possibility that the clinical needs will be modified to suit the capabilities of the investigation.

Of the indirect methods, Gee oculoplethysmography and supraorbital Doppler are clearly superior to the other plethysmographic methods and the former is the only method currently available that is capable of assessing the collateral capacity in the presence of carotid artery occlusion.

Positive test results of either of these are indicative of the presence of a high-grade stenosis or occlusion. The high false-negative rate, however, precludes its being a useful screening tool. None of these methods is accurate for identifying minimal disease and therefore cannot differentiate normal from abnormal. In addition, no information regarding lesion morphology can be identified because of their fundamental physiologic basis. The major advantage of these methods, however, is found in the relatively inexpensive nature of the instrumentation required, which is not beyond the financial capabilities of most vascular laboratories.

Of all the currently available direct methods, continuous wave Doppler examination of both the common and internal carotid arteries, with subsequent quantitative waveform analysis is a very safe, accurate and cheap method of detecting cases of high-grade stenosis. False-positive results with this examination are generated by lack of control over the angle of the incident Doppler beam, whereas false-negative results are likely to occur in the presence of occlusion.

The duplex systems using B-mode imaging and flow mapping in combination with spectrum analysis, are the most accurate methods currently available for identifying disease regardless of the severity. The former is more accurate for diagnosing occlusions and also in examining patients in whom anatomic variations exist. This capability is achieved at a significant increase in instrumentation costs and the individual laboratory must realistically assess their needs for a noninvasive testing method. A major deficiency of both of these methods is their current reliance on physiologic data and the lack of information obtainable regarding lesion morphology. Systems using a combination of high resolution B-mode and high quality pulsed Doppler appear to offer the best capabilities for detecting both stenosis and lesion morphology (Figure 1).

Digital subtraction methods have been promoted as a means of overcoming the deficiencies of the noninvasive methods without the morbidity and occasional mortality of conventional intraarterial studies. This argument has a number of obvious fallacies: The method is invasive; the resolution of such studies is inferior to that of conventional arteriography and is limited by the eventual intraarterial dye concentration, which is itself limited by current technology; single plane views only are obtained when the arteriographic standard has been biplane views; meaningful information regarding the intracerebral circulation cannot be obtained due to vessel overlap, and the mortality and morbidity of conventional cerebral arteriography have steadily declined to the point where it is now a very safe investigation in the hands of experienced radiologists. Despite these deficiencies, this method has a number of attractive features as previously outlined.

Finally, conventional cerebral arteriography remains

the standard for detecting both the severity and the morphology of bifurcation disease, the major limitations being the inherent observer variability related to a current lack of useful quantitative methods of reporting and the albeit small morbidity. The use of digital subtraction technology in the area of intraarterial studies offers the possibility of significantly reducing morbidity, particularly that related to contrast dosages. Although the arteriographic techniques are the best methods of identifying lesion morphology, the accurate detection of ulceration remains beyond the capability of all forms of testing. In this regard, only irregularity of lesions can be detected with any degree of certainty.

How, then, are these tests best utilized in a clinical setting to ensure that the maximum amount of relevant information is obtained with the least morbidity and at lowest cost?

Clinical Application

Before the availability of noninvasive testing, the evaluation of a patient who was suspected of having cerebrovascular insufficiency was based on neurologic symptoms and findings from a physical examination and contrast cerebral arteriography. Precisely locating lesions responsible for cerebral ischemia was not possible using patient testimony and neck examination alone, and whereas contrast arteriography was an appropriate diagnostic study in patients with hemispheric or monocular ischemic symptoms, its use as a means of screening patients who had nonhemispheric symptoms or an asymptomatic neck bruit was not appropriate. Noninvasive tests were developed to improve clinical diagnostic accuracy and reduce the morbidity and the cost of patient evaluation. The clinical application of noninvasive testing methods and the role of arteriography can be individualized in patients according to the presence and character of symptoms and signs, the physiologic and anatomic information required and which cerebrovascular examination is available and cost-effective.

Symptomatic Patients

Hemispheric symptoms. It is generally accepted that patients with definite hemispheric transient ischemic attacks, or monocular blindness, should be considered candidates for standard contrast arteriography. This view has emerged because of the understanding that transient ischemia of the carotid artery is frequently caused by embolization of thrombus formed on proximal atherosclerotic plaques. Investigators correlating ischemic neurologic symptoms with lesions found on arteriography have concluded that ulceration is a greater risk factor for stroke than is hemodynamically significant stenosis.[8] The same investigators also concluded that ulceration can occur in the presence of relatively minimal disease. The indirect physiologic tests (periorbital Doppler examination, oculoplethysmography), which detect only severe occlusive disease, are, for the reasons noted above, inadequate methods of identifying those patients who have potentially symptomatic lesions and thus should be considered candidates for arteriography.

The direct physiologic methods using flow pattern analysis are sensitive to both moderate and severe occlusive disease at the carotid bifurcation, but even the most sensitive noninvasive method (duplex scanning with sound spectral analysis) lacks sufficient specificity to permit its use in place of arteriography in the evaluation of a symptomatic patient. At present, it is not appropriate to use only noninvasive testing as a means of selecting patients who have focal neurologic symptoms for contrast arteriography.

Digital subtraction arteriography as a means of evaluating symptomatic patients suffers from the same limitations that apply to duplex scanning, in that the resolution is not good enough to exclude minimal disease. In a population of symptomatic patients, however, about half will have high-grade stenosis[8] that is readily identified by both methods and the other half will require high-resolution techniques to detect vessel irregularities. If one assumes that, because of its morbidity and higher cost, traditional intraarterial contrast arteriography should be done only when the information required from such a study cannot be obtained in any other way, one may realistically wonder whether there is a means of selectively using arteriography in a symptomatic patient population.

A positive noninvasive test that is capable of identifying severe occlusive disease (greater than 50% diameter reduction) with a high degree of accuracy—that is, with a low false-positive rate (duplex method)—can be readily confirmed using digital subtraction arteriography, which is also accurate in identifying the presence of high-grade stenosis. This approach would obviate the necessity for conventional cerebral arteriography when there is complete agreement between digital subtraction technique and a sensitive noninvasive test such as duplex scanning. Theoretically, this would reduce the need for conventional studies to about half of symptomatic patients. When the two tests disagree, standard cerebral arteriography would then be done. Conventional cerebral arteriography would also be required for those in whom the noninvasive test is either normal or shows evidence of minimal disease. In this setting, a high-resolution study would be required (Figure 9) and digital subtraction arteriography would not be satisfactory.

Small ulcerated plaques, not visualized by conventional arteriographic studies, may be detected by high-resolution B-mode ultrasound imaging.[47-49] The relatively benign natural history of patients with symptoms and normal findings on arteriograms[50] suggests that arteriography is of sufficiently high resolution to identify those patients at greatest risk, and further evaluation with the high-resolution B-mode systems is not likely to alter the therapeutic approach.

While noninvasive identification of internal carotid occlusion in the past would have obviated the necessity for arteriography, the development of a superficial temporal-middle cerebral artery bypass procedure[51] for

possible cerebral revascularization has necessitated that even patients with internal carotid occlusion be assessed as to their suitability for surgical reconstruction. In these circumstances, accurate visualization of the middle cerebral and superficial temporal vasculature is a prerequisite and this information can only be obtained with conventional intraarterial studies. Thus, the identification of occlusion by noninvasive testing in these patients would serve as an indication for subsequent evaluation with conventional intraarterial contrast arteriography.

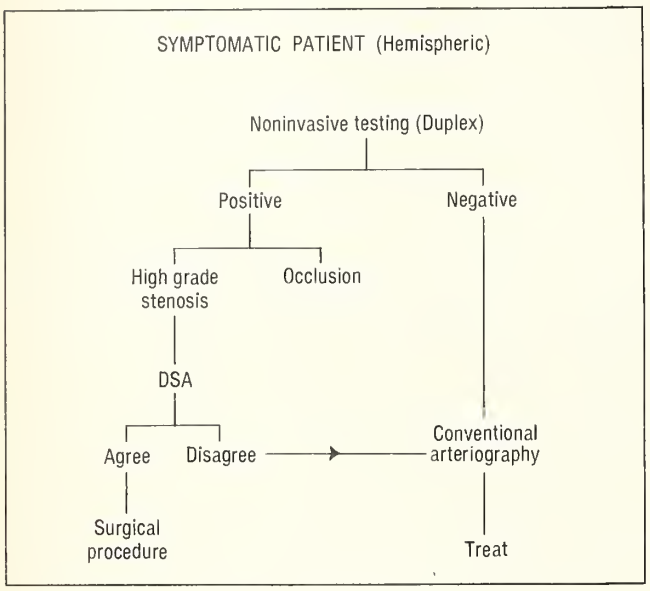

Figure 9.—Algorithmic approach for the evaluation of symptomatic carotid artery disease using the three modalities, noninvasive studies, intravenous digital subtraction arteriography (DSA) and standard conventional arteriography.

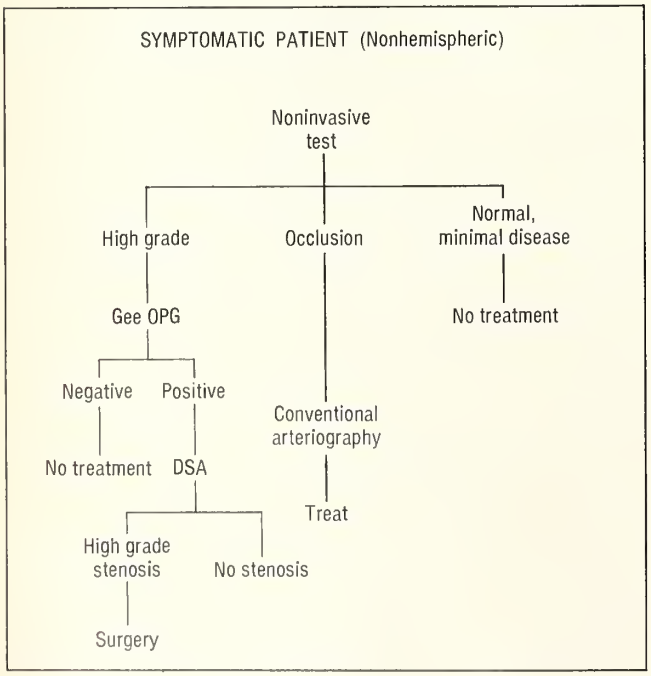

Figure 10.—Algorithmic approach for the evaluation of patients with new localizing symptoms using the same modalities as in Figure 9. OPG = oculoplethysmography, DSA = digital subtraction arteriography.

Nonlocalizing symptoms. As many as 30% of all patients referred to a vascular laboratory will have nonfocal neurologic symptoms as the reason for referral. In these patients, the cause of symptoms is thought to be due to flow-reducing lesions and not embolization. Arteriography may be avoided if a noninvasive test that has a low incidence of false-negative results for hemodynamically significant disease gives negative results. While the presence of a hemodynamically significant internal carotid artery stenosis is one of the important prerequisites in this symptom complex, the second relates to the inability of the intact cerebral vasculature to compensate for the presence of stenosis. Pressure oculoplethysmography is capable of determining this capacity of collateral circulation and has been shown to be predictive of those patients who will have relief of symptoms following carotid endarterectomy.[35] Thus, patients with a high-grade stenosis and nonfocal symptoms who have evidence of adequate collateralization could be spared the need for subsequent arteriographic evaluation as the likelihood of surgical relief from carotid endarterectomy would be minimal (Figure 10).

Asymptomatic Patients

Neck bruits are present in 4% of the population above the age of 50 years[52] and this is the most common mode of presentation of asymptomatic patients to a vascular laboratory. One is justified in asking the question whether this finding is sufficient indication for arteriography without noninvasive testing. Whereas some studies have reported that such patients do have a greatly increased risk of stroke,[53,54] other prospective studies have suggested that this is not so[55] and the presence of a neck bruit rather identifies a patient at risk of death from myocardial infarction. The key factor in unraveling such a case, in determining whether or not such patients are likely to be at greater risk, is to determine if they have disease of the internal carotid artery. Clearly, those patients with transmitted bruits and with bruits originating from the external carotid artery are not at risk and there is therefore a need to use the presence of a cervical bruit as an indication to determine whether or not there is disease in the internal carotid artery. What, then, is the best method for obtaining this information given the constraints of accuracy, cost and patient comfort? Clearly the major question is whether one should use noninvasive tests or digital subtraction techniques. It is becoming clear that the duplex systems are at least as accurate as digital subtraction arteriography in identifying high-grade stenosis and occlusions and the former can be done at a lower cost and with much less patient discomfort. In centers where duplex systems are not available, digital subtraction arteriography is likely to be the primary method of evaluation, in spite of in-

creased costs and patient discomfort, because of the overall greater accuracy compared with the other forms of noninvasive testing. Evaluation of a patient with a neck bruit will result in a variety of findings, with subsequent treatment modalities being determined by these findings (Figure 11). The approach can also be applied to those patients in whom incidental disease is found.

Unilateral high-grade stenosis. The natural history of unilateral internal carotid artery stenosis remains unknown and therefore the decisions regarding management are often emotionally rather than rationally based. Prospective studies of patients with unilateral stenosis suggest there is a very low (1% to 2%) incidence of sudden, unheralded stroke.[56,57] This observation had influenced us in the past four years to adopt a nonoperative approach and to urge a patient to report the development of focal symptoms. As stated earlier, internal carotid artery disease is only one of the factors predisposing to the development of ischemic cerebral infarction, with another being the state of the collateral pathways. In one series,[53] patients with carotid artery disease and poor collateral compensation were at a significantly greater risk of subsequent stroke when compared with patients with good collateral circulation. There may, therefore, be a role for Gee oculoplethysmography in the assessment of those patients to determine the collateral status. If an aggressive surgical approach is advocated in these circumstances, one must be mindful of the approximate 15% chance that asymptomatic stenosis is likely to recur.[58] We feel this price is too high in patients who are asymptomatic and have a low stroke potential. If the development of symptoms is used as justification for operation, only 15% of patients will require operative treatment over a three-year follow-up.

Unilateral occlusion and contralateral stenosis. One of the major benefits that accrues from the evaluation of the entire extracranial system is that significant, unsuspected disease will be detected. Patients who have this pattern of carotid artery disease have been reported as having a 3% stroke rate per year over a four-year follow-up, much higher than that expected in the normal population.[59] Because of this proved risk, we proceed with arteriography before doing thromboendarterectomy of the stenotic vessel. The role of an extracranial-intracranial bypass procedure in this setting remains unclear. If these patients are to be identified, it is essential to use a technique that is capable of detecting both high-grade stenosis and occlusions and one of the duplex systems provides the best means of achieving these goals.

Bilateral high-grade stenosis. The natural history of patients with this distribution of disease is not well documented but is likely to be similar to that of patients wih unilateral occlusion and contralateral stenosis. Identification of these patients is an indication for arteriography and consideration of endarterectomy of the internal carotid artery supplying the dominant hemisphere.

Bilateral disease (less than 50%). This group of patients remains one of the most difficult in whom to make rational decisions. Here again, the natural history of this type of case is unclear with the potential importance in determining this natural history shifting from the significance of high-grade stenosis to the potential

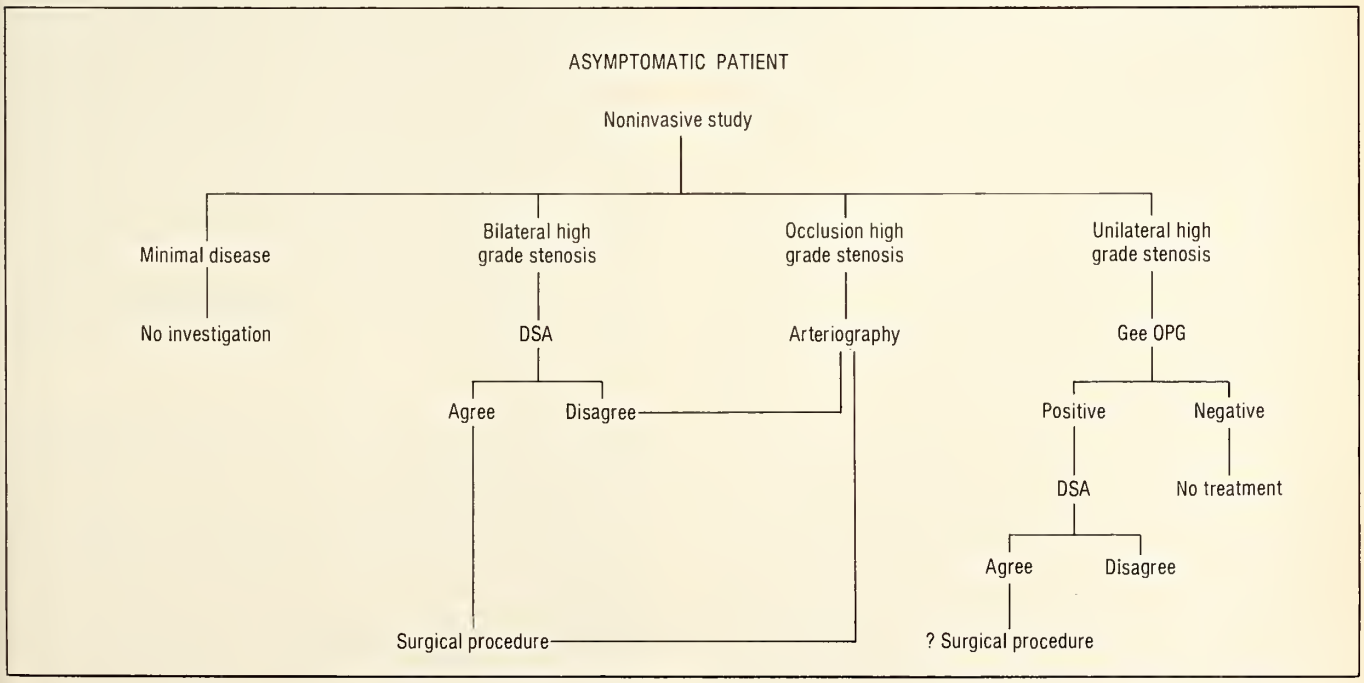

Figure 11.—Algorithmic approach for the evaluation of patients who are asymptomatic in whom disease is detected. DSA = digital subtraction arteriography, OPG = oculoplethysmography.

for embolization from irregular lesions. While it is recognized that irregular lesions occur more frequently than smooth lesions in symptomatic patients, the prognosis of irregular lesions in asymptomatic patients remains undetermined. Some studies have suggested that gross lesion irregularity is an important risk factor in asymptomatic patients,[60,61] whereas other studies have not been confirmatory.[62] If this is a major risk factor that influences a physician's decision regarding a surgical procedure, exclusion of gross lesion irregularity could only be obtained with contrast arteriography. We do not believe the identification of bilateral minimal disease is an indication for this investigation.

Preoperative screening. The remaining area in which noninvasive testing has been liberally used is in the screening of patients before major cardiovascular procedures. This approach was based on the belief that perioperative stroke was precipitated by thrombosis superimposed on high-grade internal carotid artery stenosis. The pathogenesis of perioperative stroke in these patients, however, remains unclear and it is of interest that as techniques of cardiopulmonary bypass have improved, the incidence of neurologic deficits has declined. This suggests that microembolization as a consequence of cardiopulmonary bypass is probably the most potent mechanism for producing this complication.

Results of prospective studies in which carotid artery disease has been detected with direct methods in asymptomatic patients undergoing cardiopulmonary bypass suggest that there is little correlation between the presence of severe carotid artery disease and the incidence of subsequent neurologic complications.[62,63] While there appears to be little justification for the routine screening of such patients, knowledge of the presence of severe carotid artery disease may contribute in a positive way to the careful anesthetic management of such patients. In addition, the identification of severe diffuse disease may prompt consideration of the need for a carotid artery surgical procedure in selected circumstances only.

Summary

The initial impetus for the development of noninvasive methods of detecting carotid artery disease was the morbidity associated with cerebral arteriography, though technical improvements in this area have resulted in a significant decline in the complication rate to the point where it is now a very safe investigation.

Despite this, it is clear that the noninvasive approach to the diagnosis of carotid disease has achieved a valuable position as part of the investigative armamentarium of physicians treating such patients. The major difficulty with the application of this technology is the number of methods that are available and the attendant difficulty of trying to decide which test or tests to use. The use of multiple tests as a means of overcoming the deficiency of any one test is not justified, even though instrumentation costs may be low with this approach. This approach has been responsible for justifiable criticism of the noninvasive methods because of the cost of testing borne by patients. If one attempts to balance the suitability of testing with instrumentation costs and wishes to use a single form of testing for all circumstances, clearly the duplex scanning methods offer the greatest possibility of detecting all degrees of disease. While the initial expense of this instrument is significant, the benefits conferred by having a highly accurate method of detecting carotid artery disease under all circumstances with a relatively low cost for a single test over time will provide the highest quality of care and cost effectiveness.

There are, however, circumstances in which the cost of such instruments is beyond the capabilities of small institutions or individual practitioners and, in those circumstances, the acquisition of simple continuous wave Doppler provides an accurate, cost-effective method of screening for patients who have high-grade stenosis. While the accuracy obtainable with this technique is not comparable to the accuracies obtained with duplex scanning, if an operator is aware of the limitations, it can be a very useful screening device.

Of the remaining methods, Gee oculoplethysmography provides an additional benefit of assessing collateral pathway capacity in patients with disease. It is not yet clear whether this may be a useful way of differentiating asymptomatic patients into high- and low-risk stroke groups but our current knowledge suggests that evaluation of this factor, at least, in addition to detecting carotid artery disease, may be important.

Finally, the availability of digital subtraction technology will result in the widespread application of the technique in detecting carotid artery disease. There is no doubt that it will be overused, as have been the noninvasive testing methods, and it therefore becomes the responsibility of the individual physicians caring for these patients to determine the realistic role of these modalities. This particular technology is not likely to overcome or replace either the noninvasive methods or standard cerebral arteriography. With time, a realistic place for its use will be found that will result in an augmentation of our current knowledge of carotid artery disease. Perhaps the major benefit to be accrued from the digital subtraction techniques is in their application to standard contrast arteriography and the avoidance of the problems associated with large doses of contrast media.

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Specialty Conference

Common Psychiatric Disorders in Elderly Persons

Discussant
JEAN GOODWIN, MD, MPH

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine.

JEAN GOODWIN, MD, MPH:* Traditionally psychiatrists have been known for their lack of interest in the elderly.[1] Freud at age 50 wrote, "Old people are no longer educable,"[2] and our country's Medicare system has taken Freud quite literally, severely limiting coverage for all types of psychiatric care. Thus, although 11% of the population is older than 65 years, only 2% of psychiatric outpatients are in this age group,[3] despite the fact that elderly people have a higher incidence of psychiatric disorders. More alarming is the estimate that between two thirds and three fourths of elderly nursing home residents are prescribed psychotropic drugs, almost entirely without benefit of psychiatric consultation.[4]

Today, psychiatry as a discipline is less disposed to ignore elderly persons than it once was. Developmental psychiatrists like Erikson have made a start in describing the positive personality changes that take place with age.[5] The traditional view has been that this stage in life is dominated by loss of function: decreased perception in all sensory fields, decreased reaction time, decline in new learning, decrease in extraversion, decline in facial recognition and decline in frequency of orgasm.[6] However, former child therapists, like Erikson, perceive potentials as well as problems in this developmental stage.

Freud's views to the contrary, the work in their 70s and beyond of Sophocles, Galileo, Verdi, Tolstoy, Einstein and Chagall and others attests to the rich creative possibilities in this age group. Had Titian not been carried off by the plague in his 90s, he would probably still be with us, painting ever more insightful portraits of men and of gods. The developmental assets responsible for the creative productivity in old age include new executive capacities of the personality, increased contact with inner resources through reminiscence that leads to a strong sense of personal integrity and increased gender bimodality that allows women more opportunities for managerial and political functions and allows men to become more openly emotional, sensual and nurturant.[5,7,8]

Biological psychiatrists, as well as developmental theorists, have helped reinvolve the field of psychiatry in geriatric issues through their interest in the brain biochemistry of dementia and in the mechanisms that underlie the increased vulnerability to affective disorders with increasing age.

In this discussion, four common psychiatric disorders in elderly persons will be reviewed: dementia, depression, alcoholism and paranoia. Each of these diagnoses can be documented in 1% to 10% of the elderly, and each is a more important public health problem for older than for younger populations. Dementia significantly affects 3% to 10% of the population older than 65 years; as many as 25% of the elderly will do poorly on specific psychologic tests of memory.[9] In all, 1% to 3% of the elderly will have a severe depressive disorder; 10% to 25% will score as significantly dysphoric on distress scales.[10] Alcoholism is another common psychiatric condition in elderly persons, affecting 0.5% to 2.5%. A similar percentage of elderly are diagnosed as having a paranoid condition, although a

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much larger group—15% to 20%—score as highly suspicious on psychologic testing.[6]

Dementia

The criteria for the preautopsy diagnosis of primary degenerative dementia have been defined as follows: (1) insidious onset and progression of symptoms of cognitive dysfunction; (2) negative findings on laboratory studies, which should include complete blood count, urine analysis, serum chemistries (SMA-12), serum folate and vitamin B_{12} levels, thyroid screen, VDRL, chest x-ray, electrocardiogram, electroencephalogram and computed tomographic scan; (3) a global dementia with relatively greater impairment of nonverbal than verbal abilities; (4) pronounced recent memory impairment, and (5) cerebral atrophy or ventricular enlargement beyond age expectancy.[11] This last is confirmatory of dementia but neither necessary nor sufficient to make the diagnosis. Some patients who meet these criteria will have multiinfarct dementia. This latter subgroup of patients usually has associated hypertension, diabetes or other vascular disease, as well as focal neurologic signs, and experiences a more stepwise course of cognitive deterioration.

Many physicians feel they need not consider the diagnosis of dementia in a patient who is oriented to time, place and person. Listening to a family's story provides a far better screening test than a cursory test of orientation. Judgment, mood and affect, memory and concentration are affected by dementia long before orientation becomes a problem. The following typical family's story shows how personality changes predate orientation loss in a moderately demented patient.

Five years ago, the patient was forcibly retired for reasons never adequately explained. He used to be fun to be around, now he just sits. He talks less and less. The family at first attributed these changes to depression, because of the loss of his job. He has begun to insist on an invariable daily routine, and becomes angry when this is disturbed. He does not seem to follow family conversations any more, and interrupts with inappropriate comments. He seems puzzled and vague, but denies having any problem.

The patient thus described was perfectly oriented on cursory examination. Deficits became apparent on more subtle mental state examination—questions regarding time of day and the date of a recent event and asking that he draw a map of his home. This patient also scored poorly on several standardized mental state tests, including the 30-question test developed by Jacobs and co-workers.[12] Results of neurologic and neuropsychologic examination were consistent with the diagnosis of Alzheimer's disease.

Patients and families often assist physicians in minimizing cognitive deficits. They understandably resist facing the finality of a loss of neurons. They will also have a complex set of alternative explanations and feelings about the personality changes that have marked the early years of a dementing process. Despite these resistances, a family needs to know the diagnosis as clearly and as rapidly as possible. Alzheimer's disease, the neuropathologic process found in 60% of the cases of dementia in elderly persons, is often a progressive, life-shortening condition.[13] A family needs to make plans to care for a patient during a possible downhill course that may end with the patient cachectic and bedridden. Also, the diagnosis can often rescue a patient from a situation in which everyone is becoming more and more angry with him or her. Even physicians rarely consider delirium or dementia as the cause of frustrating behavior and will automatically assume that the afflicted patient is uncooperative or lazy.[14] Such assumptions through the years before dementia is diagnosed can leave families with serious burdens of guilt. A family needs to be educated. Perhaps the single most important factor is that new learning is the most severe incapacity in dementia. If a family absorbs this fact, many problems are avoided, such as moves or unmanageably long trips for a patient, and the family can substitute environmental manipulations for the inevitably frustrating attempts to force-teach a patient.

In this country, overdiagnosis of dementia is as much a problem as underdiagnosis. It is estimated that 10% to 30% of elderly outpatients diagnosed as having Alzheimer-like dementia actually have other potentially treatable disorders. Most commonly overlooked are pseudodementia due to depression, chronic toxic reaction from drugs, an alcohol-related dementia, other dementing illness due to medical problems (often thyroid disorders, nutritional deficiencies or cancer) and other dementing disorders due to neurologic disease such as epilepsy, Parkinson's disease, tumor, normal-pressure hydrocephalus and subdural hematoma.[15] Important in clarifying the diagnosis is a careful interview in which information is elicited about alcohol history, prior mood disorders, family history of mood and cognitive disorders, trauma history, current drug use and sexual history (a positive VDRL in old people means syphilis, rather than anything more esoteric).[6]

Psychiatrist Barry Reisberg[16] recommends the following mnemonic to physicians who, in the middle of the night, may need to recall the diffierential diagnosis of dementia:

*D*rugs and alcohol
*E*motional disorders
*M*etabolic and endocrine disorders
*E*yes and ears (sensory loss)
*N*utritional deficiency and normal-pressure hydrocephalus
*T*umor and trauma
*I*nfection
*A*rteriosclerotic complications

In most studies, depression is the condition most frequently misdiagnosed as dementia. Depressed patients are vague, unresponsive, inattentive and make many errors on formal tests of cognition. The presence of a personal or family history of mood disorder, and a more subacute clinical course may be a clinician's only clues that depressive pseudodementia is the problem. Some psychiatrists have suggested that the dexamethasone-suppression test might be useful in these

situations in identifying the cortisol hyperresponsiveness that often accompanies depression. However, because cortisol hypersecretion accompanies physical illness and cachectic states, lack of cortisol suppression by dexamethasone may be a less specific marker for depression in ill older patients than in younger populations.[17] The situation is complex: not only can primary depression masquerade as dementia, but as many as 20% of patients with a primary dementia will have a secondary depression.[15] Treating these latter depressions is a critical part of good clinical management, but does not mean that these depressed, demented patients had been misdiagnosed.

Perhaps one reason physicians have difficulty diagnosing dementia is that they do not give themselves enough time. Because of the therapeutic nihilism that surrounds the diagnosis of dementia, physicians may refer a patient elsewhere after deciding that dementia is the problem and thus miss the follow-up information that is so important in confirming any diagnosis.

Therapeutic nihilism deprives a physician of many satisfactions apart from the lack of opportunity to confirm or to question the diagnosis. Families need three to six months to accept the diagnosis, and the physician who continues to work with a family during this time can establish a collaborative relationship. Again, pediatricians and child therapists often have a more intuitive grasp of the kind of care needed in these developmental crises: the care-giver needs support, optimally from other care-givers in similar situations, as in an Alzheimer's support group; the patient needs fluids and nutrition, affectionately provided, and the family needs information and support to construct a stable environment for the patient that will allow optimal functioning. We often imagine orienting interventions for a patient as consisting of shaking the person periodically and shouting at him or her the date and the name of the institution. This is just as unpleasant and disruptive as it sounds. What is profoundly orienting is to be surrounded by one's own possessions and by people whose intact memories of you are fond. Families need support in recognizing that they are more likely to provide this special environment than is a nursing home.

A physician can be useful in providing medication as well as advice and support. Multivitamin tablets, plus supplemental vitamin C, will help prevent secondary deterioration due to the nutritional deficits that may result from the poor eating habits of demented patients.[18] Also, as mentioned above, secondary depression either in a patient or in caretakers deserves to be actively diagnosed and treated.

Several pharmacologic substances have been shown to improve performance in patients who have dementia. Dihydrogenated ergot alkaloids are the most widely used.[19,20] Of 22 well-controlled studies of these drugs, all report test scale improvement in mental alertness, orientation, recent memory, motivation, locomotion and other variables. Improvement is most pronounced in patients who have mild to moderate dementia, but insignificant in patients with severe impairment. The optimal dose of these drugs has not yet been established, but many studies report good results at levels of 4.5 to 6.0 mg per day.[21] Academic medicine has been disapproving of this treatment, in part because of difficulties in evaluating the effect on a patient, but also because the completely unknown mechanism of action of the drug makes it seem irrational and magical.[22] Nonetheless, in contrast to hyperbaric oxygen, psychostimulants such as methylphenidate hydrochloride, and the neuropeptides (adrenocorticotropic hormone [ACTH], melanocyte-stimulating hormone [MSH] and vasopressin) tried thus far in dementia, dihydrogenated ergot alkaloids seem of practical help to patients and only very rarely produce unacceptable side effects.

Another drug, piracetam, has a similarly mysterious mechanism of action and produces similarly positive effects on elderly patients with mild to moderate memory impairment. Piracetam is a derivative of the neurotransmitter γ-aminobutyric acid (GABA).[19]

Current research on the mechanisms of dementia should eventually provide rationales for the therapeutic effects of dihydrogenated ergot alkaloids and piracetam. Research has been difficult because there is no exact animal model for Alzheimer's disease. The types of dementia found in Down's syndrome, in Guam-Parkinson disease, and in pugilists provide the closest human models. The best current hypothesis about mechanisms postulates that dementia results from deficiencies in cholinergic transmission in the brain.[23] The activity of choline acetyltransferase, an enzyme involved in the synthesis of acetylcholine, is greatly reduced in the brains of Alzheimer's patients as compared with age-matched controls, and a positive correlation has been found between the degree of cognitive loss and the degree of choline acetyltransferase loss in patients who have dementia. Furthermore, in young volunteers given scopolamine, an acetylcholine-receptor blocker, the same kinds of deficits in recent memory develop as found in Alzheimer's patients. In several studies aged subjects have shown pronounced improvement in memory when given physostigmine, a substance that inhibits the breakdown of acetylcholine. The fact that cholinergic receptor activity is not decreased in an Alzheimer's patient offers hope for therapeutically bypassing the cholinergic deficit. Although in vitro studies indicate that increasing brain choline level can increase the synthesis of acetylcholine, a number of studies, including data from the University of New Mexico Aging Project, indicate that simply feeding choline or lecithin to aging humans does not lead to improved memory.[24] Some clinical trials indicate, however, that when piracetam plus choline are given together, some Alzheimer's patients respond with significant improvement and with significantly higher choline levels.[23] It may be that dihydrogenated ergot alkaloids and piracetam act to improve oxidative metabolism in the brain and that this change in metabolic efficiency acts at several levels: perhaps increas-

ing choline uptake or increasing production of coenzymes to remedy the defect in production of acetylcholine.

Depression and Alcoholism in Elderly Persons

Depression is defined as a persistently dysphoric or sad mood, with loss of pleasure in usual pastimes. To be classified as depression, this mood change must last for at least two weeks and be accompanied by at least four of the following: (1) poor appetite or weight loss, (2) insomnia or hypersomnia, (3) loss of energy or tiredness, (4) psychomotor agitation or slowing, (5) loss of pleasure in usual activities or decrease in sexual drive, (6) feelings of self-reproach or excessive guilt, (7) diminished ability to concentrate and (8) suicidal ideas, wishes or attempts. The symptoms must not be due to dementia, schizophrenia or paranoia.[10]

When a cross-section of elderly persons was tested for depression in the Duke Longitudinal Study of Aging, 3.7% were found to have a major depressive disorder requiring treatment. Another 4.5% had dysphoric mood but without vegetative signs, and another 6.5% had dysphoric mood only but in a setting of severe health problems. Loss of vision was prominently associated with sadness in this group.[10]

Sadness, like cognitive dysfunction, is not a normal finding in old age and, when accompanied by vegetative signs, should be actively treated. A timely response to dysphoric symptoms is critical because of the high risk of suicide in the elderly, particularly in those with concurrent physical disease.

Treatment is not without problems, however. The tricyclic antidepressants have prominent anticholinergic side effects, a serious problem for an aging cerebral system that may already be marginally deficient in cholinergic function. The half-life of these drugs is increased in elderly persons and this contributes to a sensitivity to sedating and hypotensive side effects that can result in cerebrovascular accidents or traumatic falls and fractures. A good rule of thumb for elderly patients is to start giving tricyclics and other antidepressants at about a third the dose recommended for younger patients. Desipramine hydrochloride, a tricyclic with low anticholinergic and sedating effects, may ultimately prove a good first choice for treating elderly depressed persons. A dose of 25 mg each night is a reasonable starting dosage.[4]

When side effects prevent the attainment of adequate dosage levels to stop depression and to prevent recurrences, other types of antidepressants should be considered. The use of monoamine-oxidase inhibitors makes some pharmacologic sense in elderly patients because there is a steady rise with age in the activity of the enzyme monoamine oxidase, and this has been suggested as a mechanism for the increased risk of depression with age.[25] The risk of hypertensive crisis with these drugs must be weighed carefully, however, especially in elderly patients who have a baseline hypertension. Antidepressant treatment with methylphenidate (Ritalin), or electroconvulsion, are other options for a physically frail elderly depressed patient.[4]

A careful history will reveal prior episodes of mania in some elderly depressed persons. Mania itself may be hard to recognize in the elderly, as some of us younger physicians automatically dismiss obnoxious loquacity as normal in our elderly patients, just as we may dismiss sadness or memory loss without recognizing them as significant symptoms. Manic-depressive illness can be a complex management problem in old age. More than 20% of these patients present with cognitive deficits, as well as mood swings.[26] Lithium carbonate must be used at a third to half the usual dose because of decreased lithium clearance in aging kidneys.[1] Respiratory depression is another potential problem with lithium treatment.[27]

Alcoholism is often associated with the self-treatment of sad and dysphoric moods. Also, alcoholism and depression tend to occur together in families; it is helpful to ask about a family history of mood swings and alcohol use at the same point in an interview. Most elderly alcoholic persons started overusing alcohol before age 50, but increasing age leads to recognition of the problem as an aging alcoholic person becomes more susceptible to the central nervous system damage associated with the drug and more exposed to hospital admission-precipitated withdrawal syndromes. Alcohol withdrawal, which may be a problem in as many as 20% of elderly persons in hospital,[6] is one of the few indications for the use of minor tranquilizers in this age group. These medications are likely to cause oversedation and delirium because the half-lives of some minor tranquilizers are measured in weeks in the elderly; tissue sensitivity is also increased by twofold to threefold.[4] When absolutely necessary, diazepam can be used briefly in an elderly person with alcoholism at doses of 2 mg twice a day.

Paranoid Symptoms in Elderly Persons

Perhaps the best way to understand the gamut of paranoid symptoms in the elderly would be to spend several days interviewing "bag ladies" and other elderly transients. Here one may find a former university professor who has always been somewhat intolerant of the demands of conventional living and who has adopted a simpler life-style, much as Diogenes opted for his barrel and as Hindu elders opt for a wandering life carrying a beggar's bowl.[28,29] Don Quixote is another literary example of a thoughtful elder who chose life on the road. One will meet bag ladies who describe being driven from their home by a wicked neighbor; others will talk more vaguely about enemies and will appear to be hearing voices.

For many of these people, the psychiatric diagnosis is less clear than are the human needs. The following is an illustrative report of a case.

The patient, a divorced 67-year-old retired accountant, immigrated to this country from Germany in the 1930s. He consulted his physician because of sadness after a romantic snub from a woman friend. The physician prescribed methylphenidate, 40 mg per day. The patient began to hear people on the

street talking about him, mistaking him for a famous Nazi war criminal. He left his home of 20 years and embarked on the life of a hobo. A seriously mutilating self-slashing brought him to psychiatric attention. Phenothiazines were substituted for methylphenidate, psychotherapy was begun and he was placed in a supportive boarding home; however, he continued to hear voices for the first six months of treatment. His family history was that three of his six sibs had been institutionalized for long periods with diagnoses of schizophrenia. The patient had led a very isolated life, his marriage lasting only three months. After one year, he was asymptomatic without the use of phenothiazines and was teaching himself Spanish in order to read Don Quixote in the original.

What was the diagnosis in this case? Does the patient manifest what European psychiatrists call late paraphrenia? This diagnosis describes the first appearance in late life of the classical symptoms of schizophrenia in persons who may be biochemically susceptible but who have been protected from breakdown by other well-functioning aspects of personality.[30] Or can the clinical picture be explained simply on the basis of drug toxicity? Or is the patient suffering from chronic schizophrenia, a condition that eluded diagnosis until he reached age 67? Or is he making an existential last stand for love, power and adventure, even though he is old, poor and an outsider?

More important than these nuances of diagnosis is the necessity for swift therapeutic action in these cases. Loss of the home will be just as disastrous for a paranoid elderly patient as for an elderly demented patient; both types of patients need a physician who is willing to work hard to preserve a patient's territory. "Shuttle diplomacy" between a patient and the "enemy," usually a neighbor, may be more critical than antipsychotic agents in restoring equilibrium. Thioridazine hydrochloride (Mellaril), 25 to 50 mg a day, or haloperidol (Haldol), 2 to 4 mg a day, would be reasonable antipsychotic choices.[4,31] A complete physical examination is always necessary; impairment of any system used in maintaining vigilance—that is, hearing loss, vision loss or concentration deficits—may trigger a paranoid reaction.[32] The establishment of a trusting psychotherapeutic relationship, financial help, housing help and information—all may assist in reestablishing a patient's sense of safety.

Conclusion

Dementia, depression, alcoholism and paranoia are more likely to occur in a patient older than 65 years of age and are less likely to be accurately diagnosed and treated than in younger patients. Psychiatric treatment, like plastic surgery or surgical treatment for incontinence, can be a critical part of an older person's determination to remain in contact with the human race.[33] Physicians will find it worthwhile struggling to arrange such treatment, even though insurance plans, always, and families and psychiatrists, sometimes, may be uncooperative. Now that the average life expectancy for a 75-year-old is ten more years, it seems more important than ever that patients in this age group who have serious psychiatric symptoms obtain expert and focused help in living.

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Medical Staff Conference

Liver Transplantation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The University of California at San Francisco has had a long-standing interest in liver transplantation and has been active in research in this field. Our discussant for this conference is Dr Ira S. Goldman, who is Assistant Professor of Medicine in Gastroenterology at the University of California, San Francisco, and who performs most of his clinical duties at the San Francisco Veterans Administration Hospital. Dr Goldman's topic is the current state of liver transplantation.*

DR GOLDMAN:† It has been stated by some that the human soul resides in the liver. Whether or not that is true, it is true that the liver is an organ vital to life and, in cases of advanced liver disease, transplantation seems to offer the only hope for prolonging life. Although in the past 20 years much progress has been made, successful liver transplantation with significant prolongation of life has been difficult to achieve. Liver transplantation has only recently been put in the public spotlight, with congressional committees publicly considering funding for transplantation and television news shows devoting entire segments to the discussion of liver transplantation. I will review the current state of liver transplantation, with the hope of providing a better understanding of its background and history, indications, surgical and immunologic problems and prognosis and future prospects for those currently undergoing liver transplantation.

Two different forms of liver transplantation have been used clinically. With *orthotopic liver transplantation,* a patient's diseased liver is removed and replaced with a donor liver (homograft). In the other approach, known as *heterotopic* (or accessory) *transplantation,* a patient's liver is left in place and an extra liver is inserted at an ectopic site. Orthotopic transplantation seems to be the more promising procedure, making up well over 90% of liver transplants thus far.[1]

Welch first described the placement of heterotopic liver transplants in dogs in 1955,[2] and five years later orthotopic liver transplantation, also in dogs, was successfully done by Moore and colleagues.[3] Since then hundreds of experimental studies in various animal species have been conducted that have contributed to our understanding of the technical problems of transplantation and the features of rejection following liver transplantation.[4]

In all species thus far studied, liver grafts are rejected less aggressively than other organs. In pigs and rats, this has been especially pronounced. In rats, the degree of rejection seems to be closely related to the similarity of the strains between donor and recipient, which suggests that immune-response genes may play an important part.[5,6]

Furthermore, work by Zimmerman and co-workers this past year[7] has also shown that prolonged survival of orthotopic allografts in rats is dependent on the similarity of the strains of the animals involved, indicating a range of recipient immune responsiveness to transplantation antigens. Their work further suggests that the graft itself is involved in the immunologically specific reduction of recipient alloreactivity. Both soluble major histocompatibility antigens and antigen-antibody complexes have been found in long-term surviving liver recipient rats, and it may be these complexes that possess the observed immunosuppressive properties.

The significance of this is that because the liver is rejected less aggressively than other organs, lower doses of immunosuppressive drugs are required and thus complications can be reduced considerably, especially in the pediatric age group.

Liver transplantation was first attempted in humans by Starzl at the University of Colorado in 1963. The first patient who underwent an orthotopic transplantation died, as did six others at several centers during

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the next year. Consequently, clinical trials were halted for three years. In 1967 the first extended survival of a human liver recipient was achieved. The patient, an 18-month-old girl, lived for more than 13 months before dying of metastasis from hepatocellular carcinoma, the disease for which she had originally been treated.[8]

Heterotopic liver transplantation was first done clinically by Absolon and associates in 1965,[9] but one-year survival was not achieved until 1973 by Fortner's group in New York City.[10]

The demonstration of its feasibility, however, did not make liver transplantation a widely used clinical procedure. Clinical trials were continued, but only on a limited basis due to the disparity between the moderate success rate and the immense requirements for personnel and financial resources. Equally prohibitive are the difficulties in defining the indications for transplantation, the lack of an artificial liver support device and the complexity and severity of surgical, immunologic and infectious problems after transplantation.

Transplant Centers

There are two major transplant centers in the world. One group is headed by Thomas E. Starzl, MD, initially working in Denver and now at the University of Pittsburgh,[8,11] and the other, instituted in 1968 by Drs R. Y. Calne and Roger Williams, is a joint program conducted between the University Hospital at Cambridge and King's College Hospital in London.[6,12,13]

Other centers that have reported six or more cases include those headed by Pichlmayr in Hanover, West Germany, with 68 cases[14]; Krom in Groningen, Holland, with 18 cases[15]; Houssin in Paris; Wolff in East Germany and Hong in the Republic of China. In the United States, clinical transplant programs are also active at the University of Minnesota and the University of Tennessee.[8]

Indications and Contraindications

In theory, any patient dying of liver disease might benefit from a liver graft, but in practice some general criteria, such as the factor of age, have emerged. Whereas Starzl's group considers children as well as adults under 50 years of age as potential candidates,[8,11] Calne and Williams have avoided pediatric transplants because of a shortage of pediatric liver donors and the side effects of long-term steroid use in this population, and they recommend assessing biologic rather than chronologic age in their adult patients.[6,12]

Older patients are not considered good risks, as they frequently cannot withstand the side effects of the intensive immunosuppression. The prospects for treating children with a variety of liver disease have improved, however, since the risks of long-term, high-dose steroid therapy have been reduced with newer immunosuppressive agents, such as cyclosporine.

The major contraindications to transplantation include portal vein thrombosis, metastatic carcinoma, major systemic infection and systemic arterial hypotension. Relative contraindications include alcoholism, as alcoholic patients tend to be unreliable; extensive prior abdominal operations because of adhesions; acute fulminant liver failure because the prognosis is so difficult to assess and the operative risks too high, and liver disease not severe enough to warrant transplantation.[8] Hepatitis B surface antigen positivity in a recipient is not a contraindication to transplantation[16]; however, chronic hepatitis B infection has recurred even with the use of hyperimmune globulin at the time of transplantation.

TABLE 1.—*Indications for Orthotopic Liver Transplantation in 103 Adult Patients**

	Percent Patients
Cirrhosis	47
Primary biliary cirrhosis (N=13)	
Cryptogenic (N=11)	
Chronic active hepatitis (N=9)	
Sclerosing cholangitis (N=4)	
Alcoholic (N=4)	
Secondary biliary cirrhosis (N=3)	
Other (N=4)	
Primary hepatoma	34
Cholangiolar carcinoma	7
Hepatic metastasis	5
Budd-Chiari syndrome	5
Extrahepatic biliary atresia	2

*Cambridge/King's College Hospital Series, from Williams et al.[13]

Adults

In adults, most liver grafts have been done in patients who have nonmalignant, nonalcoholic cirrhosis. The most common indications among adult patients with cirrhosis in Calne's series are primary biliary cirrhosis, cryptogenic cirrhosis and chronic active hepatitis (Table 1).[13] The other major category is primary malignancy of the liver. Although the incidence of tumor recurrence is almost 60%, results have been especially favorable in the fibrolamellar form of hepatoma, which seems to be late in spreading.[8,16-18] Patients who have cholangiocarcinoma that is confined solely to the liver may also be considered for transplantation. The indications for carrying out liver transplantation in adults in Starzl's series are very similar to those of Calne and Williams.

Children

In children, liver transplantation has been done most commonly for biliary atresia, chronic active hepatitis and hepatic-based inborn metabolic diseases (Table 2).[19] What is particularly intriguing about the hepatic-based metabolic diseases is that cures have been effected with transplantation. Success has been achieved with several such metabolic diseases as α_1-antitrypsin deficiency, hereditary tyrosinemia, sea-blue histiocyte syndrome and Wilson's disease.

In Starzl's series,[20] all four patients with α_1-antitrypsin deficiency assumed the normal donor phenotype or

their serum α_1-antitrypsin returned to normal levels after transplantation. One patient with glycogen storage disease had normal carbohydrate metabolism postoperatively. Normalization of serum tyrosine and urinary metabolites occurred in a patient who had hereditary tyrosinemia, and patients with sea-blue histiocyte syndrome and Wilson's disease each had reduction of neurologic deficits.

Timing of Transplantation

Because of the risks involved in transplantation, the timing of the operation requires careful thought. A patient's disability from liver disease should be great enough and the prognosis so limited that, in comparison, the risks of transplantation become acceptable. On the other hand, by the time a patient shows signs of advanced liver failure, the chances of surviving a surgical transplant procedure may be greatly reduced.[16] Still, more than 50% of those accepted for liver grafting die before a donor liver becomes available.[6]

Much of the difficulty in determining when to transplant would be reduced if accurate tests of hepatic reserve or those of true liver *function,* analogous to the creatinine clearance for assessing renal function, were available. There is, however, no equivalent simple way to measure hepatic function or reserve. Similarly, there is no artificial hepatic support device analogous to the kidney dialysis machine; if such a device existed, we would have the luxury of attempting liver transplantation under much more controlled conditions.

TABLE 2.—*Indications for Transplantation in 112 Pediatric Patients (≤18 yrs)**

	Percent Patients
Biliary atresia	55
Inborn metabolic errors	19
Chronic aggressive hepatitis	13
Neonatal hepatitis	3
Secondary biliary cirrhosis	3
Hepatoma	3
Congenital hepatic fibrosis	1
Others	3

*From Malatack et al.[19]

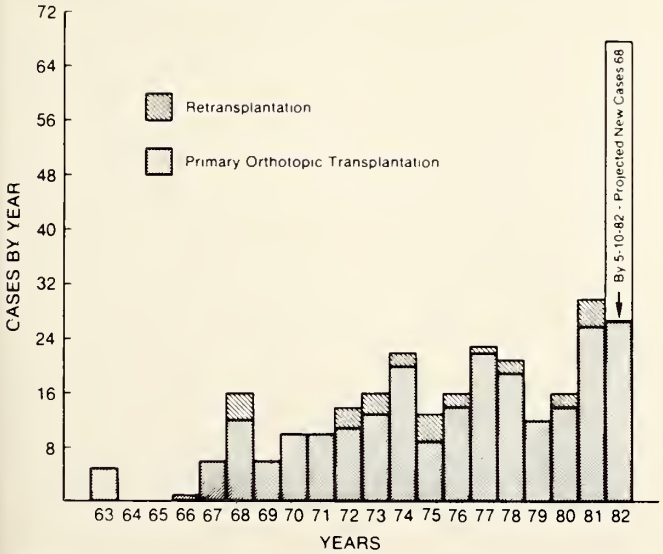

Figure 1.—Yearly number of liver transplantations at the University of Colorado (1963 to 1980) and the University of Pittsburgh (1981 to 1982). (Reproduced from Starzl et al[8] with permission of the authors and publisher.)

Preoperative evaluation requires an in-hospital investigation. In the case of cirrhosis, it is essential to determine that the portal vein is patent by using mesenteric angiography or splenoportography; thrombosis of the portal vein is a contraindication to transplantation. In cases of malignancy, the diagnosis of primary malignancy of the liver must be confirmed histologically, and involvement of both lobes confirmed; otherwise, partial hepatic resection would be the procedure of choice. Chest and bone radiographs, radionuclide bone scans, lymphangiography and computed tomography have been recommended as part of the work-up to exclude extrahepatic metastasis.[16]

Of about 500 orthotopic liver transplants that have been done worldwide to date, more than 400 have been done by Starzl's and Calne's groups. As can be seen from Stazl's recent experience of the past year or two (Figure 1), the number of transplantations being carried out is increasing rapidly.[8]

The urgent need of most patients receiving a liver transplant and the time constraints of liver preservation have precluded systematic attempts at tissue typing.[8] With the random donor-recipient pairing thus far used, good matches at the human leukocyte antigen (HLA)-A, B and DR loci have not been obtained. Hepatic transplantation has been done without adverse effect in the presence of recipient antidonor antibodies, which cause hyperacute rejection in renal homografts.[21] ABO blood group transfusion principles are generally accepted practice. Starzl has reported a few cases of transplantation across ABO blood groups,[8] though this is rarely necessary.

Donor Operation

Procuring a sufficient number of donor livers has been one of the most significant problems for the groups attempting transplantation, in common with those attempting renal transplantation.[22] Although the kidneys are not compromised by liver removal, there has been some reluctance on the part of those transplanting or procuring kidneys to have the liver removed from the same donor.[23] The removal of the donor liver is an operation that itself takes two to three hours.

Since the acceptance of brain death criteria, well-preserved organs can be obtained that are relatively free from the damages of ischemia. Starzl preserves livers by rapidly perfusing them with a cold electrolyte (Collins') solution and has stored them up to 12 hours.[8] Calne's group uses a plasma protein solution and has stored donor livers for up to ten hours.[6]

Because bile is such an irritating substance, especi-

ally to ischemic tissue, bile is removed from the large bile ducts and gallbladder by irrigation with cold plasma to prevent sloughing of biliary mucosa from bile left in the biliary tract.

Recipient Operation

The recipient operation is technically the most difficult, and is also the most dangerous hurdle a patient has to overcome.[8] The diseased liver is removed following cross-clamping and dividing the hepatic artery, portal vein and inferior vena cava above and below the liver. The more recent use of venous bypass from femoral to upper extremity or jugular vein, and an intervening oxygenator, has minimized problems related to hemodynamic instability during cross-clamping of the major vessels.

Size matching of the donor liver to the recipient is important to prevent mechanical respiratory compromise and to permit closure of the abdomen. Vascular reanastomosis is accomplished first, followed by reconstruction of the biliary tree. The spleen was removed in most of the patients transplanted before 1979, in part to achieve better immunosuppression, but mainly to relieve hypersplenism and leukopenia that prevented the use of azathioprine or cyclophosphamide. With the advent of cyclosporine, formerly called cyclosporin A, splenectomy has been mostly discontinued.

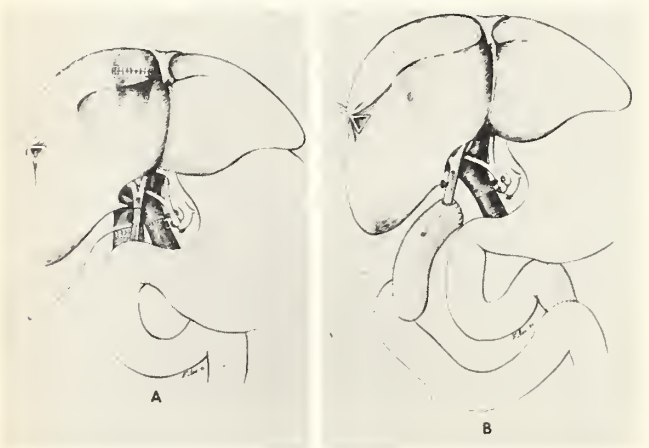

Figure 2.—Completed orthotopic liver transplantation. **(A)** Biliary tract reconstruction with choledochocholedochostomy. **(B)** Biliary reconstruction with choledochojejunostomy, using a Roux limb. (Reproduced from Starzl et al,[8] with permission of the authors and publisher.)

TABLE 3.—*Operative and Postoperative Complications**

Operative	
Hemorrhage	Vascular anastomosis
Hypotension	Air embolism
Hyperkalemia	Donor-recipient size mismatch

Postoperative	
Early	*Late*
Biliary obstruction plus fistula	Rejection (acute and chronic)
Sepsis and opportunistic infection	Biliary obstruction
Gastrointestinal hemorrhage	Sepsis and opportunistic infection
Intestinal perforation	Tumor recurrence
Respiratory insufficiency	Recurrent hepatitis
Irreversible ischemia	

*From Grendell.[16]

Biliary tract reconstruction was considered the most difficult part of liver grafting and accounted for most fatal complications in early trials.[1] The incidence of bile fistula and biliary obstruction leading to sepsis has been reduced with modern techniques. Starzl considers duct-to-duct anastomosis with a T-tube stent, as illustrated in Figure 2-A, to be the procedure of choice. When this is not feasible, such as in cases of biliary atresia wherein the recipient residual bile duct is short, the duct is anastomosed to a Roux limb of jejunum, as shown in Figure 2-B.[8]

Since 1976 Calne has used a technique in which the homograft common duct and gallbladder are anastomosed into a common channel or conduit, and then connected either to the recipient common duct or a Roux limb of jejunum.[24]

Perioperative Complications

Operative complications accounted for the poor survival rates in early trials, some of which are listed in Table 3.[16] Hemorrhage could be massive, and patients often received as many as 50 units of blood during a single transplant procedure. Hypotension and the necd for venous bypass after clamping the major vessels have been mentioned. Life-threatening hyperkalemia occurred intraoperatively due to massive efflux of potassium into the systemic circulation because of ischemia of either the recipient or the donor liver. Vascular anastomoses frequently clotted; air embolism with severe neurologic sequelae from air left in the donor liver, and donor-recipient size mismatch were but a few of the early problems.

Postoperative complications can be broken down into an early and a late phase as shown in Table 3.[16] Some of these have already been alluded to. Sepsis and opportunistic infection were major causes of death in half of Starzl's first 93 patients. At autopsy, almost 20% had evidence of systemic fungal infection.[25]

Gastrointestinal hemorrhage occurred in 23% of Starzl's first 150 patients, with a mortality of 85%.[26] Peptic ulcer disease was the most frequent cause. Intestinal perforation from biliary anastomoses now occurs less frequently, and respiratory insufficiency from an oversized homograft has been mentioned.

All of the above perioperative complications are potentially reversible except for ischemic injury of the homograft or early loss of its blood supply. In such cases, retransplantation is the only hope.

Late complications include rejection (both acute and chronic), biliary obstruction, sepsis, tumor recurrence and recurrent hepatitis.

Immunosuppression

Initially, immunosuppression in liver transplant recipients was accomplished using the same regimen as

TABLE 4.—*Clinical Immunosuppressive Drug Regimens**

	Year of Study
Azathioprine and steroids	1963
Thoracic duct drainage as adjunct	1963
Antilymphocyte globulin as adjunct	1966
Cyclophosphamide substitute for azathioprine	1970
Cyclosporine (cyclosporin A) alone	1978
Cyclosporine and steroids	1980

*From Starzl et al.[8]

for kidney transplants. "Double-drug" therapy with azathioprine and prednisone was the first successful immunosuppressive regimen used. Between 1963 and 1980, several alternative programs were introduced (Table 4), all of which were essentially modifications of the original azathioprine-prednisone regimen.[8] Thoracic duct drainage, antilymphocyte globulin and substitution of azathioprine with cyclophosphamide were all tried. Although rejection had generally been fairly well controlled with these regimens, the immunosuppressive therapy frequently led to septic complications. New and more promising hope for reducing the risks of immunosuppression came with the discovery of cyclosporine.

Cyclosporine is an extract from the fungi *Cylindrocarpon lucidum* and *Trichoderma polysporum*. It was first used clinically by Calne and White,[27] who quickly discovered its adverse side effects, namely those of nephrotoxic and hepatotoxic reactions. Both of these appear to be dose-related and reversible.[28] Hepatotoxic response, which occurs in about 20% of cases, is rarely serious enough, however, to necessitate discontinuation of the drug.[29]

Cyclosporine acts by depressing both humoral and cellular immunity, with a preferential and quick reversible action against T lymphocytes. These effects are not accompanied by the bone marrow depression that so frequently limits the doses of azathioprine and cyclophosphamide.

Calne and Williams usually wait until renal and hepatic function have stabilized before starting a regimen of cyclosporine, which permits a reduction in steroid dose to as low as one fifth of the prior dose used. Starzl, on the other hand, starts giving his patients cyclosporine on the day before the operation, along with large but rapidly tapered doses of prednisone. Doses are individualized so as to control rejection but minimize side effects.[8]

Rejection

Rejection of homografts still occurs, despite the use of any of the immunosuppressive regimens. This is particularly important because histologically recognizable rejection occurs in up to 50% of cases. There are no reliable liver function tests for expeditiously diagnosing functional failure of a homograft nor is there an artificial support device or readily available second organ (as with the kidney) to rely on when a homograft fails.

The clinical signs and symptoms of rejection are nonspecific and include fever, vague upper abdominal pain and loss of appetite. Ascites and hepatomegaly are often found on physical examination. Laboratory findings are equally nonspecific and include elevations in the serum bilirubin, alkaline phosphatase and aminotransferase values and prothrombin time. Radionuclides, such as those used in liver scanning, are poorly concentrated.[8]

Because all of these findings are so nonspecific, differential diagnosis from biliary obstruction, viral hepatitis or recurrence of an underlying disease (such as primary biliary cirrhosis) is at times difficult. The distinction is clearly important, however, as rejection requires *increased* immunosuppression, whereas biliary obstruction or viral hepatitis could have disastrous results unless immunosuppression is *decreased* and appropriate interventions made. Radiographic visualization of the biliary tree to rule out obstruction is mandatory before increasing immunosuppression. Similarly percutaneous needle biopsy of the liver has been invaluable in distinguishing rejection from other diseases.[16]

Characteristic findings of liver transplant rejection include infiltration of portal triads by mononuclear cells, mild centrilobular necrosis with bile stasis and destruction of small bile ducts in a pattern suggestive of primary biliary cirrhosis. As rejection progresses, further hepatocyte loss, fibrosis and arterial intimal thickening occur, all of which become characteristic of chronic rejection. Fennell and colleagues[30] have recently described the histologic similarity of nonsuppurative destructive cholangitis seen in chronic rejection of human liver allografts, primary biliary cirrhosis and chronic graft versus host disease. Earlier reported recurrence of primary biliary cirrhosis after transplantation[31] may have been the nonsuppurative destructive cholangitis associated with chronic rejection.

Survival Rates

Starzl attributes the recent pronounced improvement in his results to the use of cyclosporine and divides his results into the precyclosporine and postcyclosporine eras. The 170 operations done between 1963 and 1979 were reported by Starzl as three separate series. All patients were treated with azathioprine and steroids, or a variety of other adjuvant treatments as outlined earlier. Of these 170 patients, the one-year survival averaged 33%, and of these one-year survivors, 41% died in the next year and 59% lived for between 2.5 and 13 years; 20 patients have survived for more than five years.[8]

Half of these same 170 patients were younger than 18 years and, for unexplained reasons, this group had a 10% survival advantage when conventional immunosuppressants were used. Since the introduction of cyclosporine, however, survival rates of the two groups have been comparable.

Since the introduction of cyclosporine in 1980, almost 100 patients have received liver transplants, 67

of which are well documented (see Figure 3, top line). The middle line represents the 170 patients in the three series before the introduction of cyclosporine; the bottom line shows the survival of patients in Calne and Williams's series.

In the cyclosporine series, most of the deaths occurred in the perioperative phase. The actuarial survival of cyclosporine-treated patients has *doubled* the observed survival in the pre-cyclosporine era, with a current one-year survival rate of about 70%.[8]

Retransplantation

What is done if a transplant fails? With the lack of an artificial hepatic support device, *retransplantation* is the only alternative. In all, 27 patients since 1968 have been regrafted. Two patients have received three orthotopic liver grafts. Unfortunately, only 6 of these 27 patients have had significant prolongation of life with retransplantation.[8]

In Calne and Williams's series,[12] 127 livers had been transplanted as of the end of 1982, with an experience

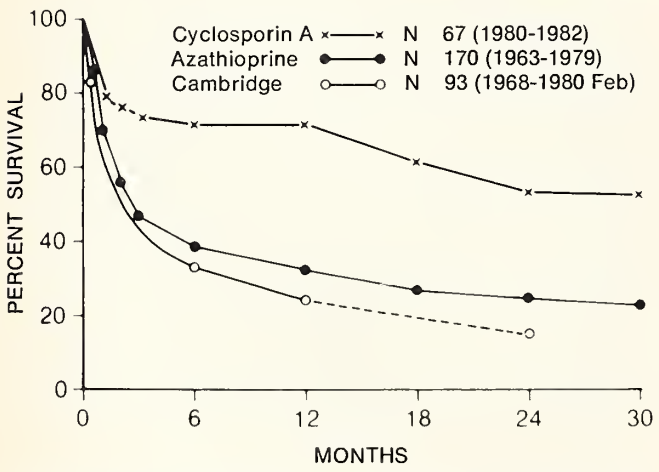

Figure 3.—The actuarial survival of patients treated with cyclosporin A (cyclosporine) and low-dose steroids compared with the actual one-year survival obtained with conventional immunosuppression (azathioprine) by Starzl and by Calne. (Reproduced from Starzl et al,[8] with permission of the authors and publisher.)

roughly parallel to that of Starzl. In all, 16 patients are living after more than a year and four patients longer than five years. Their longest survivor is alive seven years after transplantation.

In Pichlmayr's series[14] in Hanover, 68 orthotopic transplantations have been done in 65 patients, most within the past three years. Their transplantation data were divided into two categories (Table 5): those patients undergoing liver transplantation for tumor and those for cirrhosis. Of 20 patients in whom extrahepatic tumor was detected at the time of operation, only one survived for more than six months. In the other 17 patients without metastasis, four have survived more than one year. In the group with cirrhosis, those in whom transplantation was done under emergency conditions did not do as well as those who underwent more elective operations. Survival in the group with liver tumors confined to the liver was similar to that in the cirrhotic group in fair condition. An interesting observation from this group is that the patients who had cirrhosis seemed to undergo more severe rejection than those who had tumor.

In Krom's series in Holland,[15] 18 liver allografts were done between 1979 and the middle of 1982. In all, 13 patients are alive, of whom 4 survived for more than a year and 3 for more than two years. These results were achieved with conventional immunosuppression without the use of cyclosporine. This group is the only one, however, that has used selective *bowel decontamination,* consisting of administering broad-spectrum antibiotics as well as polymyxin B sulfate and amphotericin B before the surgical procedure. Krom attributes the reduced incidence of Gram-negative sepsis and systemic fungal infection and their improved survival rates to this decontamination regimen.

The collective experience in liver transplantation at all centers has shown a trend toward improved survival rates, as is now evident in the fact that for patients who survive the complications of the operative and perioperative periods, the one-year survival is about 70%. Furthermore, survival rates with those undergoing transplantation for primary hepatic malignancy (without metastasis) is similar to that found in patients who have cirrhosis, and survival rates have become com-

TABLE 5.—*Liver Transplantation Results in Patients With Tumor and Those With Cirrhosis**

	No. of Patients	*Survival Time (months)*				*Alive*	*Longest Survivor*
		1	*1-6*	*6-12*	*>12*		
Tumor							
Extrahepatic growth	20	8	7 (4)	4 (—)	1 (—)	(4)	2 yr
No extrahepatic growth	17	5	2 (1)	6 (2)	4 (4)	(7)	6.75 yr
Cirrhosis							
Emergency operation	19	15	2 (2)	1 (1)	1 (1)	(4)	3.25 yr
Fair condition	9	1	1 (1)	2 (1)	5 (5)	(7)	19 mos

*From Pichlmayr et al.[14] Numbers in parentheses represent patients alive at time of publication of Pichlmayr's paper.

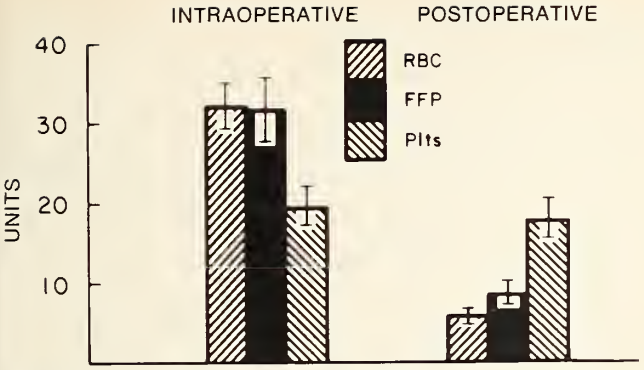

Figure 4.—Blood products used during and following liver transplantation. Bars represent means; brackets represent standard error. RBC = erythrocytes, FFP = fresh frozen plasma, Plts = platelets. (Reproduced from Van Thiel et al,[31] with permission of the authors and publisher.)

parable in adults and children since the introduction of cyclosporine.

Heterotopic Transplantation

Heterotopic grafting, an alternative to orthotopic transplantation, involves attaching an extra liver and leaving the patient's diseased liver in place. This all seems logical enough, but of nearly 50 well-documented heterotopic transplants, only two have had long-term success.[10] Theoretically, in such cases the extra liver could be construed as a temporary support organ, which can be removed later. Unfortunately, what happens clinically is that most of these accessory livers atrophy.[32]

The two primary indications for heterotopic liver transplantation are (1) small or shrunken livers, such as are seen in nonmalignant cirrhosis or biliary atresia, and (2) fulminant, self-limited disease, such as in patients with severe viral or chemical hepatitis.

One of the major by-products of research on heterotopic transplantation has been new insight into the effects of portal blood and its so-called *hepatotrophic substances* on the liver's structure, function and its ability to regenerate. These factors, which include insulin, glucagon and epidermal growth factor[33] among others, profoundly influence liver growth and regeneration.

Conclusion

Liver transplantation, especially since the introduction of cyclosporine, has become a potentially viable form of therapy. Whether the long-term results with cyclosporine continue to be as good as the initial ones remains to be seen. There are, however, some important unanswered questions: Which patient should undergo liver transplantation and when? Why are livers rejected less aggressively than other organs, and why is it that, in some species, the liver seems to be immunologically privileged? What kinds of liver function tests must be developed so that hepatic function of the recipient and donor livers can best be quantitated? And, can a temporary artificial hepatic-support device be developed?

Funding of liver transplantation is a major question. As in the past, funding is still piecemeal at best. Much of the original work was done under grants from the National Institutes of Health (NIH). Third-party payers have been inconsistent in deciding whether liver transplantation represents accepted therapy or an experimental approach. More recently, families have had to turn to individual fund-raising appeals to fund transplants for one of their members.

What is unquestionable is that hepatic transplantation should not be undertaken without full institutional commitment. The requirements for a liver transplantation program are broad: intensive-care unit beds, operating room facilities and personnel must be available at short notice; in-hospital beds and outpatient follow-up facilities must be available; medical and nursing staff must be committed to the program, and social and psychiatric support services are very much needed.[11] The drain on an institution's blood bank for a single transplant patient alone can be staggering. Figure 4 shows the *average* blood product use in transplantation.[11] One can well imagine the quantity of blood products used when one contemplates attempting even three or four transplantations a month, as Starzl's group hopes to achieve.

While the approximate cost of a liver transplantation in Pittsburgh has averaged $55,000 with a range between $23,000 and $150,000,[8] Starzl states that dying of end-stage liver disease without the hope of recovery may be even more expensive. O'Donnell and associates[34] in 1980 reported that in Boston the average cost of treating a patient with variceal hemorrhage was $35,000, and the use of any operative procedure increased the total to $53,000. At the University of Pittsburgh, the costs incurred during repeated hospital admissions of these patients, before transplantation, exceeded those incurred by transplantation itself. What is currently unknown is what the yearly follow-up costs in caring for transplant patients will be, and what economic impact this technology will have on our health care system.

There will be increasing public pressure to do liver transplantation. It is estimated by Starzl that within five to ten years, every major center for the study of liver disease will have either liver transplantation capabilities or direct access to this kind of service, and that at least 20 centers will be needed in the United States alone.[8] However, whether this can or should be achieved needs to be examined. These issues were explored at a recent NIH Consensus Conference on Liver Transplantation.[35] Useful data comparing the effectiveness of transplantation with standard medical therapy are needed. It is hoped that the NIH consensus conference and prospective clinical trials will provide some of these answers.

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Epitomes
Important Advances in Clinical Medicine

Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Exchange Transfusion in Pregnant Women With Sickle Cell Disease

THE FIRST published article suggesting that exchange transfusion might be used for prevention as well as treatment of sickle cell disease complicated by pregnancy appeared in 1963. This rather aggressive approach attempted to address the 10% maternal death rates being reported at that time and pregnancy wastage (abortion and perinatal death) that varied from 40% to 60%. Only in the past few years, however, has this modality achieved rather widespread use, which has been reinforced by recent reports suggesting an improvement in both maternal and fetal outcome. Prophylactic partial exchange transfusion (PPET) reduces the concentration of hemoglobin S by replacing it with hemoglobin A, which offers better tissue perfusion and oxygenation. Other possible advantages of this therapeutic approach include suppressed hemoglobin S erythropoiesis, an increased sense of well-being, reduced infections, reduced crises (both frequency and intensity) and improved perinatal outcome.

Despite these potentially positive factors, there are disadvantages to this approach—both real and theoretical; thus not all physicians are in accord with the recommendation for this procedure in pregnant women who have sickle cell disease. With prophylactic partial exchange transfusion, large numbers of blood cells are transfused and isosensitization remains a serious threat to patients. The other possible disadvantages include hepatitis, anaphylaxis, volume overload, hemochromatosis, premature labor and psychological dependence.

Risks are minimized by the use of washed, buffy coat-poor erythrocytes—which decreases the number of leukocytes, a very frequent cause of transfusion reactions. The risk of hepatitis is also lessened by using washed cells. Further, consanguineous donors who have no sickled hemoglobin should be used to reduce the chance of atypical antibody formation. The potential problem of iron overload seems more theoretic than real. With PPET, iron is also removed, albeit a smaller amount than that which is replaced. Women in addition are relatively protected by periodic blood loss associated with menstruation, iron loss to the fetus during pregnancy and the blood loss that attends parturition.

Most physicians thus far have used a manual method to conduct PPET, which, after hydration, involves the removal by phlebotomy of whole blood and the rather awkward replacement of packed cells containing hemoglobin A. The possibility of volume overload, although an infrequent occurrence, should not be overlooked. Moreover, with this manual method there is a permanent loss of a patient's endogenously produced plasma, platelets and leukocytes. More recently a transfusion technique known as automated erythrocytapheresis has been used. With this technique, a continuous flow system withdraws a measured volume of a patient's blood and selectively removes from it by differential centrifugation the hemoglobin S-containing erythrocytes. The patient's remaining plasma, platelets and leukocytes are returned to her circulation, along with an aliquot of hemoglobin A-containing donor erythrocytes.

As stated earlier, the risk-benefit ratio of this thera-

peutic approach is unclear and because of this a consensus development conference on this subject was convened in 1979 by the National Institutes of Health. I hope that the issues raised in this article can be answered through a randomized multicenter collaborative study such as that suggested by the consensus development conferees. HENRY W. FOSTER, JR, MD

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The G Suit in the Management of Intra-abdominal Hemorrhage

ONE OF THE most effective therapeutic procedures available to an obstetrician-gynecologist for the control of intractable abdominal hemorrhage is the gravity (G) suit. The G suit is also known as the MAST suit (military antishock trousers) and the antishock suit. It was used extensively in the Vietnam War, allowing transport time to base hospitals of severe trauma casualties and thus saving many lives. It is also used extensively throughout the United States by paramedics when transporting a patient in shock to a hospital. The G suit consists of three inflatable chambers, one for each leg and one for the abdomen. Inflation of these chambers to a pressure of 10 to 20 mm of mercury creates a circumferential compression of the vessels in the abdomen and legs, which has two effects. First, it causes a shunting of blood from the legs and abdomen to the vital structures of the head and chest; it has been estimated that an autotransfusion of as much as 750 to 1,000 ml of blood can occur depending on a patient's size and blood volume. Second, the use of the G suit has a hemostatic effect by reducing the radius and the tension of vessel walls, allowing clot formation.

The G suit's application in obstetrics and gynecology is primarily in the treatment of hemorrhagic shock. There are many clinical situations in which its use is most appropriate. One of the most dramatic is in treating shock in a patient with a ruptured ectopic pregnancy. Patients in shock respond to application of the G suit with a rise in their blood pressure and a slowed pulse rate, thus allowing time to restore blood volume and to transfer the patient to the surgery for a definitive procedure.

Postoperative bleeding due to oozing and raw vascular beds that cannot be controlled by good surgical technique and packing can be very effectively controlled by using a G suit. Some examples would be for oozing after hysterectomy in patients with extensive adhesions due to chronic pelvic inflammatory disease or endometriosis; after cesarean section for placenta previa, especially when implantation has occurred at the site of a previous scar; uncontrolled venous bleeding in a space of Retzius after suprapubic bladder neck suspensions, and after cesarean hysterectomy oozing due to the increased vascularity. By using the G suit in a prophylactic manner for 24 to 36 hours, the frequency of second operations and hematomas can be reduced.

Postpartum hemorrhage due to uterine atony may be effectively controlled by using the G suit. Patients aborting and those passing a hydatidiform mole who are hemorrhaging excessively and in shock respond to application of a G suit until definitive therapy can be implemented. Patients in septic shock without blood loss can be treated by the use of a G suit, which allows a team to implement all of the therapeutic modalities that are indicated and necessary. Patients with coagulopathies respond well to the gravity suit as a supporting modality.

The use of the G suit in many varied conditions that cause massive blood loss or shock has been extensively studied and reported. There are few contraindications for its use, the main ones being patients who have cerebral edema, pulmonary edema, congestive heart failure or bleeding above the diaphragm. The abdominal chamber should never be used for a pregnant patient.

Very few complications have been reported and the benefits can be lifesaving as well as reducing the amount of blood products needed and their associated complications. JOHN E. GUNNING, MD

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Comparative Risks of Osteoporosis and Endometrial Cancer

CESSATION OF ovarian function and the associated drop in endogenous estrogen levels lead to a variety of estrogen deficiency conditions such as osteoporosis, vasomotor symptoms, urogenital tract atrophy and psychological changes. At the same time, the incidence of endometrial carcinoma—a disease known to be related to estrogen use or estrogen production—increases, though the overall incidence of this disease is small. Of all estrogen-dependent diseases that are more or less specific to menopause, osteoporosis and endometrial carcinoma carry the greatest morbidity and mortality.

Osteoporosis affects up to 25% of all white women 65 years of age and older. The clinical implications of this disease are manifold: It is estimated that after age 45 years, 1 million women in the United States each year suffer fractures—700,000 are due to osteoporosis and half of these could have been prevented. In 1979 there were about 125,000 cases of hip fracture in older women in the United States. The cost of medical treatment of these fractures could be as high as $1 billion yearly and 15% of all women will die within three

months after a hip fracture. There is probably more than one form of postmenopausal osteoporosis and many factors play a role in its pathogenesis, such as genetic predisposition, activity, diet and body size.

Endometrial carcinoma is the most common malignant condition of the female genital tract. Every year 39,000 new cases are diagnosed in the United States and 3,000 women die each year as a result of the tumor. Genetic predisposition, parity and body size are known risk factors in this disease.

Exogenous estrogen administration has been shown to decrease the risk of the occurrence of postmenopausal osteoporosis, but increase the chance of endometrial carcinoma. In some studies endogenous estrogen levels have been found to be decreased in cases of osteoporosis of the hip and spine, whereas in many patients with endometrial cancer the levels of these hormones were increased or they were receiving estrogen replacement. This difference in estrogen levels appears to be mediated through body stature—patients who have endometrial cancer are generally obese, whereas patients who have osteoporosis have a propensity to be slender.

The risk of both postmenopausal osteoporosis and endometrial carcinoma can be decreased by estrogen replacement therapy in combination with progestins. Gambrell in a large study found that estrogen-progestin users not only had a significantly lower incidence of endometrial cancer than those using estrogens only, but the incidence was also lower than in those using no hormones. The combination therapy appears to be at least as effective in preventing postmenopausal osteoporosis. There is evidence that progestins alone have a beneficial effect on bone metabolism.

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Genital Herpes and Vaginal Delivery

GENITAL HERPES is thought to affect millions of women in the United States. Although more epidemiologic data are needed, the Centers for Disease Control have presented some evidence that an epidemic occurred in the 1970s. The signs and symptoms of primary and recurrent genital herpes are well known but other problems mimic this disease and misdiagnosis is common. Until recently no well-documented effective treatment has been available. Also, physicians caring for women with herpes in pregnancy have had an increasing tendency to do a cesarean section because of the severe and devastating outcome when a neonate is exposed to this virus.

Numerous purported treatments for genital herpes have been reported over the past decade but, when tested scientifically in double-blind placebo-controlled fashion, they have proved to be ineffective. Acyclovir has recently been proved effective. This antiviral drug is a purine analogue that through a complex mechanism inhibits the replication of viral DNA. Its action is quite specific and has been well documented both in vitro and in vivo to prevent replication of both herpes simplex virus type 2 and herpes simplex virus type 1, which cause about 85% and 15% of genital herpes infections, respectively. Acyclovir is available in two forms—as a topical ointment and as a sterile powder for intravenous administration. Both the topical and intravenous forms of acyclovir are licensed for use in initial episodes of genital herpes in a non-immunocompromised patient. In severe cases the most dramatic results of treatment are seen with the use of the intravenous form. In an immunocompromised patient, either form of acyclovir is indicated for use in a recurrent or an initial episode of disease, and the intravenous form is indicated in all cases of life-threatening disease. Topical acyclovir has not been proved effective in treating recurrent genital herpes. Although the patient demand for this form of therapy in recurrent herpes is great, its use should be avoided until data prove its efficacy, as there is always the risk of resistant strains developing. Oral acyclovir, which may be available in coming months, offers the hope for a more effective but less expensive therapy for primary and recurrent disease in the future.

The most severe consequence of adult genital herpes infection is neonatal acquired infection. Most commonly acquired during labor and delivery, the disease, though rare, has if untreated a mortality rate of 85% in disseminated disease and in treated neonates continued high mortality and morbidity. In one study, in 70% of cases of neonatal herpes, the mother was asymptomatic for herpes infection at delivery. Asymptomatic viral shedding during gestation has been reported to be as high as 14%. For this reason, to decrease the incidence of neonatal disease and also the need for cesarean section in mothers at high risk of disseminating herpes infection, it is recommended that viral cultures be done on a weekly basis beginning at 32 weeks gestation and from both mother and neonate at delivery. Specimens must be taken from the cervix, vagina and vulvar sites or from affected skin surfaces below the waist. Pooled specimens are advised to decrease the cost of surveillance. If lesions occur close to term, cultures should be done every other day to determine when shedding ceases. Shedding usually ceases between the third and fifth day and rarely continues beyond the eighth day in recurrent disease. In a case of active herpes, as shown either by lesions or by a positive culture in an asymptomatic patient, cesarean section is indicated.

All pregnant women should be asked appropriate questions to elicit whether genital herpes may be a problem in their pregnancy. Patients with a history of multiple partners, other venereal disease, partners with herpes infection or a history of recurrent vulvar irritation should be followed in the above fashion. If disease

has not occurred previously, a patient should be encouraged to present within 24 to 48 hours of the onset of symptoms, when cultures are most likely to document the infection. Reliable tissue culture results may be obtained within five days and within 48 hours if immunoperoxidase staining is available. The findings of several clinical studies suggest that vaginal delivery may be done in about 70% of patients at high risk for harboring herpes infection who are followed in this manner. No cases of neonatal herpes have been reported in these studies.

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Vaginal Versus Cesarean Delivery for Breech Presentation

THE TREND TOWARD more vaginal births in cases of breech presentation is based on recent prospective and retrospective reports indicating that in selected, carefully evaluated and monitored women, vaginal delivery carries an acceptable perinatal mortality and morbidity when corrected for congenital abnormalities and prematurity. The major morbid events related to breech labor and delivery are umbilical cord prolapse, head entrapment, cervical spine injury, traumatic delivery or extraction and the occurrence of a nuchal arm or arms. Umbilical cord prolapse occurs in less than 2% of frank breech presentations, but the risk increases progressively from complete to double footling, and is highest in the single-footling presentation. Some investigators have reported that a great proportion of the cord prolapses occur in the second stage of labor. Head entrapment is most frequently encountered in a premature breech, usually when the fetus weighs less than 1,500 grams. Because of inherent errors in estimating fetal weights, a 2,000-gram cutoff would provide a good margin of safety. Cervical spine injuries are associated with an extended fetal head and excessively forceful delivery. There is general agreement that a cervical spine-mandibular angle of 90 degrees or less is *not* extended. Traumatic deliveries or extractions are usually related to overzealous efforts for a vaginal delivery in a patient who has a less-than-totally adequate pelvis, or with labor abnormalities requiring oxytocin augmentation. Brachial plexus injury may result from the management of nuchal arms; the frequency of nuchal arms seems to be increased in the hands of less-experienced operators and when the assisted breech delivery is rushed.

The following guidelines offer a reasonable approach to selecting women with breech presentation for vaginal delivery:

- Gestational age between 36 and 42 weeks.
- Estimated fetal weight between 2,000 and 4,000 grams.
- Clinically adequate pelvis confirmed by x-ray pelvimetry.
- Fetal head not hyperextended.
- Availability and use of continuous fetal monitoring equipment.
- Normal progress of labor.
- Awareness of the risk of a prolapsed cord by the entire medical team.
- An obstetrician who is experienced in vaginal breech delivery.
- The capability to do a rapid cesarean delivery exists during the entire course of labor.
- An anesthesiologist is in attendance.

As in all medical practice, management decisions are based on an assessment of the risks and benefits of a proposed procedure or treatment. We have emphasized the perinatal risks of vaginal breech delivery, but must not ignore the increased maternal morbidity and mortality associated with cesarean birth.

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Abnormal Findings on Papanicolaou Smear: Significance and Management

THERE IS overwhelming evidence accumulating that both the incidence of and mortality from cervical cancer are reduced by screening and treatment of the precursor lesions. Richart showed that squamous cell carcinoma of the cervix begins at the squamocolumnar junction of the transformation zone as a unifocal lesion that is generally well differentiated. The term "dysplasia" has been applied to this lesion. Depending on the degree of dedifferentiation of the cytoplasm of the dysplastic cells, the lesions are described as "mild, moderate or severe dysplasia." As the lesions enlarge, the cells become less differentiated, occupy a larger area of the transformation zone and may grow towards and into the endocervical canal. The end stages of the intraepithelial lesion are generally referred to as "carcinoma in situ." Richart prefers to call these lesions "cervical intraepithelial neoplasia, grades I, II or III" because he considers them continua of the same disease.

Papanicolaou originally reported his cytologic results as class I through V, but with the passage of time the different classes have acquired different interpretations. Cytopathologists are now reporting their results using narrative terms such as "mild, moderate or severe dysplasia and carcinoma in situ" or "cervical intraepithelial neoplasia grades I, II and III," and include other normal and abnormal findings, such as endo-

metrial cells. The Papanicolaou smear is but a screening test, and under ideal conditions there is a false-negative rate of 5% for intraepithelial disease and of 20% to 30% for invasive carcinoma of the cervix.

Once an abnormal result is obtained from a smear, the cervix should be examined colposcopically. The location and extent of the lesions can be delineated and possible extension towards and into the endocervical canal ascertained. Distinction can be made between intraepithelial and invasive cancer and histologic correlation can be obtained by biopsy and endocervical curettage. The technique of colposcopy is described in various publications.

When the entire lesion is visible and histologic and cytologic examinations show mild to moderate dysplasia, the treatment of choice is cryotherapy or, where available, laser evaporation. When there is disease in the endocervical canal, conization of the cervix is recommended. In cases where there is severe dysplasia or carcinoma in situ (cervical intraepithelial neoplasia grade III) and the whole lesion is visible, there is controversy whether cryotherapy or laser evaporation is appropriate, as the incidence of residual disease or subsequent invasive cancer seems higher than in those treated by conization.

The American Cancer Society has recently recommended changing the screening from one to three years, but the American College of Obstetricians and Gynecologists disagrees and recommends annual smears for all sexually active women because the risks of invasion in patients with undetected carcinoma in situ, or cervical intraepithelial neoplasia, increases exponentially as the interval between cytologic examinations increases.

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Human In Vitro Fertilization and Embryo Transfer

THE EXTRACORPOREAL fertilization of mammalian oocytes was first reported more than 20 years ago. Since that time more than ten different species of mammalian oocytes have been successfully fertilized in vitro. In the past three years, reports of successful human in vitro fertilization and embryo transfer have been received from England, Australia and the United States. The use of an in vitro fertilization and embryo transfer system to deal with various factors encountered in infertility situations is becoming more common.

Currently clomiphene citrate or human menopausal gonadotropin (Pergonal) therapy is used as the primary method to stimulate multiple follicle development and indirectly help time laparoscopic oocyte recovery. In conjunction with ovarian stimulation, patients have daily ultrasound scanning of the ovaries and serum specimens are taken for measurement of estradiol levels. Before laparoscopic aspiration, human chorionic gonadotropin is given to initiate final maturation of the oocyte.

With the use of ovarian stimulation and intravenous administration of human chorionic gonadotropin, it has been shown that laparoscopy should be done 36 hours from the time of the latter injection. The laparoscopy is done using general anesthesia and routine laparoscopic techniques. A special oocyte-aspirating system is currently being used in which a 14-gauge needle with an interlining of 18-gauge Teflon goes into a fluid trap and is connected to a wall suction set at about 150 mm of mercury negative pressure. By monitoring with combined ultrasonic and hormonal methods and with the Teflon-lined aspirating system, we are able to recover oocytes in about 85% of the follicles aspirated.

About five hours after the laparoscopic recovery of the mature oocyte, the husband is asked to produce a semen specimen. After preincubation of the sperm, 50,000 motile cells are then added to the plate containing the oocyte. At about 40 hours from the time of fertilization, the oocytes are inspected and at this time four- to eight-cell embryonic development should be observed. Once normal embryonic development is seen, transfer back into the patient's uterus is undertaken, using a Teflon catheter system.

Work on the human in vitro system began early in 1970; however, pregnancies have occurred only within the past five years. The overall pregnancy rate in any given program is about 15% to 20% of patients treated. The problems we face today with this fertility procedure are slowly being solved. The techniques that may become applicable in the near future are ultrasound-directed, needle aspiration of mature oocyte, thus alleviating the need for general anesthesia and laparoscopic aspiration. Moreover, with growing evidence of successful cryopreservation techniques in animals, the possibility of human embryo cryopreservation may become a reality. These techniques appear viable but must be tested extensively before they are available for use in humans.

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The Use of Ultrasound in Infertility Management

ESTIMATES ARE that one out of every six couples requires medical assistance to achieve a pregnancy. For most of these, where no pathologic condition exists, precise timing of ovulation is the most critical element for success. Whereas the use of drugs such as clomiphene citrate (Clomid) or menotropins (human menopausal gonadotropin [Pergonal]) often better define the ovulatory period, the more conventional mea-

sures rely upon basal body temperature charts, cervical mucus examination and previous menstrual history as guides. In some cases, hormone assays like rapid estradiol or luteinizing hormone have been of great use; even when all of these measures are used accurately, however, predicting the time of ovulation can be a significant clinical problem. Because the viable lifespan of a human ovum is 16 to 18 hours and preceding fertilization the sperm must undergo a four- to six-hour transformation termed capacitation, precise timing becomes critical.

This problem has been substantially eliminated in the past two years through in vitro fertilization programs and application of real-time ultrasound as a means of timing laparoscopic recovery of ova. Using a full-bladder technique, ovaries and their developing follicles can be readily defined in transverse and longitudinal planes. Follicular growth proceeds at a rate of 1 to 3 mm a day, with a rapid growth spurt possible some 24 to 36 hours before ovulation. Follicles are considered to be functionally mature when their maximal diameter is 18 mm or more. Follicles of this size will respond to ovulation doses of human chorionic gonadotropin (5,000 to 10,000 IU) within 12 to 36 hours after intramuscular injection.

Ultrasound used in this manner does not replace more conventional measures of impending ovulation, but it does hold the promise of better understanding of a given patient's ovarian response to natural or drug-induced signals. Completed studies suggest that its use increases pregnancy rates while shortening course of treatment.

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Changing Views on the Management of Vaginitis

THERE HAVE BEEN a number of significant advances in the treatment of infectious vaginitis in the past five years, not only through the introduction of new drugs but also by using existing drugs for new indications. In view of the fact that the three major types of vaginitis are all to some extent sexually transmitted, it is likely that the number of women seen with complaints referable to vaginitis will continue to increase.

The most common cause of infectious vaginitis is *Gardnerella vaginalis* vaginitis, previously called *Haemophilis vaginalis* vaginitis or nonspecific vaginitis. The infection is characterized by a profuse, homogeneous, adherent gray discharge that is associated with a "fishy" odor and a minimum of irritative symptoms. Although the laboratory diagnosis has relied on recognition of "clue cells" in the saline wet mount, another helpful diagnostic maneuver is the "odor" or "amine" test in which the odor of the discharge worsens upon adding 10% potassium hydroxide solution to the residue on the posterior blade of the speculum. Treatment has traditionally consisted of topically applied sulfa creams or oral tetracycline, but it is now generally agreed that these measures are relatively ineffective and that the agent of choice is metronidazole, 500 mg given twice a day for seven days to both the patient and her partner. In patients in whom metronidazole is contraindicated (such as pregnant women), cephalexin or ampicillin, 500 mg given four times a day for seven days, are secondary drugs of choice. A contrary opinion was recently given by Robbie and Sweet when they reported their reservations regarding the extensive and repetitive use of metronidazole because of its possible mutagenicity and carcinogenicity when more innocuous methods are available. They suggest that local preparations or ampicillin be used as the treatment of choice and that metronidazole be reserved for initial treatment failures.

Women with monilial vaginitis usually have vaginal and vulvar itching and burning and a nonodorous white vaginal discharge. Diagnosis is made on the basis of identification of pseudohyphae on a 10% KOH slide or with a positive yeast culture. Nystatin, which had previously been the drug of choice, has now been replaced by the more effective synthetic imidazole fungicides, clotrimazole and miconazole nitrate, which are available as creams, vaginal tablets and suppositories. Although standard therapy consists of a daily application for seven days, a recent study has shown equivalent results with twice-a-day therapy for three days, thereby giving patients a choice of regimens.

Trichomonas vaginalis vaginitis presents as vaginal itching and burning in conjunction with a foul-smelling watery discharge. Diagnosis depends on the identification of motile trichomonads on saline wet prep or a positive Diamonds culture. The mainstay of treatment continues to be metronidazole, though recent studies have shown that a 2-gram single dose is as effective as the more standard seven-day course. Because of improved compliance and minimization of the duration of side effects, most authors consider the single-dose regimen, given to both patient and partner, to be the treatment of choice for vaginal trichomonas.

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Glucocorticoids and Lecithin-Sphingomyelin Ratio

THE ANTENATAL USE of glucocorticoids to prevent respiratory distress syndrome in premature infants has accelerated over the past several years. The rationale for their use is based on several studies done of humans and animals that have shown the following: (1) Exogenously administered steroids accelerate the normal pattern of lung development, including the accumula-

tion of lamellar bodies in type II cells and the production of alveolar surfactant. In humans, glucocorticoids decrease the incidence of respiratory distress syndrome and increase survival rate for premature infants. (2) Most likely increasing concentrations of endogenous corticosteroids in an undisturbed or a stressed fetus influence lung development in the same manner as exogenously administered steroids. (3) When exogenously administered glucocorticoids are used in dosages that do not elevate fetal cortisol concentrations beyond that seen with physiologic stress responses, they present little risk to an infant. (4) Morphologic, functional and biochemical variables of lung development are more closely correlated to cortisol concentrations than is fetal age.

Although the lecithin-sphingomyelin ratio in amniotic fluid has proved to be a reliable index of fetal lung maturity, the amniotic fluid "lung profile" can more accurately predict fetal lung maturation in humans. Several studies have shown an increase in lecithin-sphingomyelin ratio after exogenous glucocorticoid administration, whereas others failed to do so, albeit noting a significant reduction in the incidence of respiratory distress syndrome and increased fetal survival. The latter findings suggested that either adequate amounts of surfactant should be present in alveoli before their appearance in amniotic fluid or that qualitative alterations in surfactant composition not reflected by the lecithin-sphingomyelin ratio have occurred. Recent findings in alloxan-treated animals show that exogenously administered glucocorticoids increase phosphatidylglycerol synthesis and reverse the functional delay in fetal lung maturity, with no significant change in surfactant content or the lecithin-sphingomyelin ratio. The above findings attest to the added advantage of using an amniotic fluid "lung profile" specifically in those clinical situations—such as a case of diabetes mellitus with no vascular involvement and Rh immunization—wherein delayed lung maturity is expected.

Studies of surfactant metabolism show that maximal beneficial effects of glucocorticoids are obtained after 36 hours of administration. Also, for continued benefit, the same dose should be repeated seven to ten days later. Of great interest are the recent observations that fetal responses to glucocorticoid administration are influenced by sex and ethnic origin.

I recommend that the use of glucocorticoids for fetal lung maturity be limited to women in premature labor whose amniotic fluid analysis is not available, or is in the immature range, and whose labor can be delayed for at least 36 hours; where immediate delivery is indicated (that as, in cases of severe hypertension or abruptio placenta), glucocorticoid administration is contraindicated. More studies are needed to define optimal mode of drug delivery, dosage, short-term maternal risks and the long-term effects on neonatal central nervous system and immune systems.

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Immunologic Thrombocytopenia in Pregnancy: Predicting Fetal-Neonatal Risks

IMMUNOLOGIC THROMBOCYTOPENIC PURPURA is a relatively uncommon disorder whose occurrence in the general population includes a significant number of women of childbearing age. As a result, obstetricians can be faced with the problem of managing such a patient during a pregnancy.

Earlier reports had suggested an increase in maternal mortality to rates as high as 14%. Similarly, perinatal death rates of 15% to 25% had also been reported, related at least in part to thrombocytopenia in neonates. This background information, as well as the absence of any more sensitive laboratory evaluation than maternal platelet count, probably contributed to the recommendation of a "prophylactic" cesarean section when the maternal platelet count was less than 100,000 per μl. More recent studies, however, that examined the immunologic mechanisms of this disorder and their application in pregnant patients, have resulted in a more selective use of cesarean section in such patients.

Immunologic thrombocytopenic purpura is caused by antiplatelet antibody of the subclass 3 of immunoglobulin G. As well, there appear to be placental receptors for the Fc portion of the IgG molecule that can account for active transport of antibody to the fetal circulation. The level of antiplatelet antibody can be measured in maternal serum with respect to both free circulating antibody and bound, or platelet-associated, antibody. In addition, the latter techniques can still be used whether a patient is in remission or has active disease, and whether or not she is receiving steroids.

In 1982 Cines and co-workers examined levels of free and associated antiplatelet antibody in 23 pregnant women. While the maternal levels of platelet-associated antibody did not correlate with thrombocytopenia in their neonates, the levels of circulating antibody were elevated in 11 women, 9 of whom had thrombocytopenic neonates (defined as having a platelet count of less than 150,000 per μl). Further, the mothers who had the highest levels of circulating antibody had the more severely affected neonates (a platelet count of less than 30,000 per μl).

In 1983 Scott and associates similarly examined circulating antiplatelet antibody levels. While they found thrombocytopenic neonates in mothers with elevated antibody levels, they also noted affected neonates in mothers whose levels were normal. They therefore also used fetal scalp blood platelet counts in 25 patients and correctly identified the five thrombocytopenic in-

fants (platelet count less than 50,000 per μl) with no complications from the technique in any of the infants.

From these reports, it would seem that cesarean section in mothers with immunologic thrombocytopenic purpura should be "selective" rather than "prophylactic" except for other usual obstetric indications. Such mothers should be evaluated for elevated circulating antiplatelet antibodies to determine the range of risk for neonatal thrombocytopenia. Further, at 3 cm of dilatation, fetal scalp blood for platelet count should be obtained and, following Scott's recommendations, physicians should select cesarean delivery of fetuses whose platelet count is less than 50,000 per μl and allow vaginal delivery when the count is more than 50,000 per μl.

Maternal bleeding complications at cesarean section are unlikely with platelet counts of 30,000 per μl or more. In mothers whose counts are less than 20,000 per μl, immediate preoperative platelet transfusions should minimize the risk of hemorrhagic problems.

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An Updated Approach to the Diagnosis of Ectopic Pregnancy

DIAGNOSING ECTOPIC PREGNANCY is difficult and the problem is missed by the initial examining physician in up to 70% of cases. The correct diagnosis, which is typically made at the time of rupture, is usually delayed for two to three weeks after a patient seeks medical attention.

In an effort to diagnose ectopic pregnancy earlier—that is, before rupture—an updated approach using the combined results of the highly sensitive serum radioimmunoassay pregnancy test and ultrasound is required. The advantages of the radioimmunoassay test over the more frequently used immunologic pregnancy test include its increased sensitivity and specificity (lack of false-positive and false-negative results) and the ability to quantitate the precise level of human chorionic gonadotropin (HCG).

Ideally, an ultrasound study should be done in patients in whom the results of the pregnancy test are known. Uterine changes are the key feature for deciding whether the pregnancy is intrauterine or extrauterine. Recent evidence suggests that it is possible to differentiate an abnormal intrauterine pregnancy or a decidual reaction of an ectopic pregnancy from an early normal intrauterine pregnancy with about 98% confidence by identifying "double decidual lines" in patients who have a normal intrauterine pregnancy. Patients with intrauterine fluid who lack this finding have either an ectopic pregnancy or an abnormal intrauterine pregnancy.

Adnexal changes are difficult to assess in patients who have suspected ectopic pregnancy because it is not usually possible to be certain that a visualized adnexal mass represents the ectopic pregnancy. Similarly, cul-de-sac fluid is also a nonspecific finding and can occasionally be due to a ruptured or hemorrhagic corpus luteum cyst.

If the ultrasound findings and HCG determination are suspicious but not diagnostic for ectopic pregnancy, a variety of tests may be required, including serial HCG determinations, repeat ultrasound examination, uterine dilatation and curettage, culdocentesis or laparoscopy.

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Editorials

America's Ways of Doing Things

We in this nation have the best health care and probably the highest standard of living in the world. Even what we call poverty bears no resemblance to the poverty to be found in many other places. This standard of living and this quality and availability of care have been achieved by changing many of the earlier American ways of doing things. In a word, as things became more complicated it was found that the earlier laissez faire ways of doing things did not work well enough. In fact the laissez faire system finally broke down and this resulted in 1929 in the Great Depression. At that time the people turned to the federal government and demanded that it do something. This change in emphasis was accomplished by the national election in 1932 which was followed by the federal interventions of the Roosevelt era and the growth of the role of the federal government in American society which continues even under the present administration. In retrospect this was a dramatic shift away from what had been the traditional American way of doing things.

The extraordinary progress in medical science and technology since World War II soon began to cause things to become complicated in health care, as they had previously in society generally, and again the people turned to the federal government. What is now often called the health care industry has come to be the most regulated industry in the nation. Again this occurred because the problems had become too complex and the traditional laissez faire approach to health care did not deal adequately with them. And this too was a dramatic shift away from what was the case in the earlier less scientific and less technological era of patient care in this nation.

This dramatic shift from private responsibility to public responsibility for solving complex problems may not at first have been fully recognized for what it is. In any event the results are beginning to become more obvious. The tools that government has to solve problems are laws, regulations that have the force of law, and money which it raises through taxes, by borrowing or by simply printing it. These tools have been used in the fullest measure for almost half a century and now the extent of their use has in turn become a major part of the problem. And as power has become more centralized in government, the people have formed themselves into hundreds if not thousands of special-interest groups, every one of which, by definition, must be a minority. The pressure exerted by these often opposing groups and the complexities of often conflicting laws and regulations can actually paralyze government decision-making and thwart effective action in the majority or public interest. In essence the evidence is accumulating that many of the problems engendered by our standard of living and the quality and availability of our health care will never be solved by reliance on government. It may be that the time is coming for another dramatic shift in America's ways of doing things. Neither the traditional laissez faire approach nor reliance on centralized government seems to work well enough.

Perhaps it is time to return at least some of the problems to the people for solution by negotiation and agreement among those most directly involved. This could be done in communities or, where appropriate, in regions or even nationally. This will result in some unevenness in the solutions, but in health care at least the solutions offered by government have led to unevenness and certainly to something less than equality. In a sense this could be a return to the earlier American concept of the town meetings where decisions were made and problems dealt with by consensus and agreement among those most directly involved and in terms of the resources available to the community from whatever source. It is interesting to note that health care now pervades almost every element of American society and has become an integral part of our standard of living. It has been found that neither laissez faire nor the regulatory approach—nor even government money—has been able to cope adequately with its problems or develop truly lasting or satisfying solutions. It would seem that health care, pervasive as it is throughout our society, could begin to lead the way for what must sooner or later be another dramatic shift in the American way of doing things. Physicians are a minority in health care, and the health care industry is a minority component of the American standard of living, but we are a relatively organized minority with a broad base in American life, and we are among the first to recognize that while some things are best left to laissez faire, and that some things in a complex interdependent society are best regulated by government, there are yet some things that are showing themselves to be beyond the ability of either approach to deal with successfully. Health care, in many of its aspects, is surely one of these. Perhaps it is time for the ball to come back into the people's court—in health care at least.

MSMW

Noninvasive Assessment of Carotid Artery Disease

Diagnostic methods and therapeutic alternatives for cerebrovascular disease are rapidly evolving. In the past decade we have witnessed a remarkable development of sophisticated noninvasive diagnostic techniques that not only have improved our ability to unobtrusively detect carotid artery disease, but also have permitted improved understanding of the natural history and efficacy of treating carotid atherosclerosis. Improvements in inva-

sive diagnostic radiology have led to rapid proliferation of digital subtraction techniques that permit safer and less painful visualization of the major cerebral vessels with intravenous injection of contrast material. Indeed, the widespread application of digital subtraction angiography has led many physicians to question the relative role of noninvasive diagnostic techniques in the evaluation of patients with symptomatic or asymptomatic cerebrovascular disease. Finally, a variety of therapeutic alternatives have recently been developed, including newer antiplatelet agents, improvements in carotid surgical monitoring and operative techniques and skillful application of extracranial-intracranial bypass procedures to revascularize cerebral territories previously inaccessible in the presence of thrombosis of the extracranial internal carotid artery. With these many advances, it is no wonder physicians are confronted with a bewildering number of diagnostic and therapeutic alternatives in a patient who may have cerebrovascular disease. Yet, logic in the management of such patients must prevail to satisfy the demands of cost effectiveness in the allocation of these available resources.

It is, thus, timely that Bandyk and Thiele review the principles and applications of the current noninvasive, semi-invasive and invasive diagnostic techniques of evaluating carotid artery occlusive disease. They emphasize an integrated algorithmic approach to the most appropriate diagnostic modality based upon a patient's symptoms and extent of detectable carotid artery disease. The authors have presented an up-to-date, state-of-the-art approach that should be studied seriously by all physicians involved in the diagnosis or treatment of patients with carotid atherosclerosis. I am in general agreement with their recommendations. I would like to emphasize some points of agreement and discuss some areas of controversy. And then I would like to comment on the most important area of the relative roles of noninvasive diagnostic techniques versus intravenous digital subtraction angiography and to emphasize the changing role of noninvasive methods in symptomatic versus asymptomatic patients.

Bandyk and Thiele point out the importance of differentiating normal from abnormal carotid arteries. The ability to only noninvasively detect advanced disease is no longer an acceptable goal for a noninvasive vascular laboratory. Patients with cerebral symptoms due to extracranial carotid atherosclerosis may have emboli from lesions that do not reduce pressure or flow and, thus, may not be detected by indirect screening techniques such as periorbital Doppler ultrasound or ocular plethysmography. Nevertheless, such lesions can usually be detected using more sensitive direct carotid screening techniques, including continuous wave or pulse Doppler ultrasound with spectrum analysis or high-resolution B-mode imaging devices. Although physicians previously believed that all symptomatic patients deserved angiography, the current option of doing intravenous digital subtraction angiography has created a new role for a noninvasive laboratory in screening patients for extracranial carotid artery lesions of sufficient extent to be detected by the newer radiographic methods. More will be said about this important subject later.

A second goal for a noninvasive laboratory is the definition of the integrity of the cerebral collateral circulation, particularly via the circle of Willis. Indirect noninvasive techniques provide physiologic information during brief periods of carotid compression that may be of predictive value in distinguishing patients whose carotid lesions may be compensated for by collateral circulation versus those persons who are dependent on flow through the diseased vessel. Such physiologic information may not be gleaned from the morphologic images of an arteriogram. Knowledge of cerebral collateral circulation is of particular importance to a surgeon in planning for a possible indwelling shunt during carotid endarterectomy. The integrity of the circle of Willis may also be of importance in predicting the natural history of patients with asymptomatic carotid disease and the possible need for prophylactic carotid endarterectomy. Bandyk and Thiele appropriately emphasize the value of this information in managing asymptomatic patients or patients who have atypical, nonlateralizing symptoms.

Despite the attractiveness of intravenous digital subtraction angiography, the limitations of this technique and, indeed, the limitations of conventional intraarterial contrast arteriography have only recently been emphasized by several investigators. The group at the University of Washington has been instrumental in carefully evaluating the intraobserver and interobserver variability of interpretation of carotid arteriograms. The surprising variability of diagnostic interpretation is aggravated by the reduced image resolution of intravenous digital subtraction angiography.

In addition, the problems of the nonselective nature of the study, the limitations of views, motion artifacts and the need for repeat intraarterial study in a finite percent of cases all are contributing to a more tempered enthusiasm for this diagnostic study. Nevertheless, there are clear-cut roles for intravenous arteriography and the authors provide a sound approach to the use of this new imaging modality based on the results of noninvasive studies.

There are a few areas in which I would take minor issue with their statements. They suggest that continuous wave Doppler ultrasound, while simple and less expensive, does not provide the diagnostic accuracy of combined B-mode Doppler ultrasound (duplex scanning). While audible interpretation of continuous wave Doppler signals is sensitive only to more advanced disease, the use of spectrum analysis with continuous wave Doppler interrogation of carotid arteries has provided a sensitivity and specificity that approach that reported with duplex scanning.[1,2] Although duplex scanning is recommended as being the best diagnostic device for most vascular laboratories, the expense, complexity and technical challenges of this instrument limit its widespread application. I feel that many vascular laboratories are more easily applying continuous wave Doppler ultrasound with real-time spectrum analysis with results that are similar to that of duplex scanning. Nevertheless,

in the final analysis, high-resolution B-mode imaging coupled with Doppler ultrasound remains the noninvasive diagnostic standard for evaluating extracranial carotid artery atherosclerosis.

Bandyk and Thiele suggest that the oculopneumoplethysmograph of Gee is the only method to evaluate cerebral collateral circulation; however, Bone and coworkers described the use of periorbital Doppler ultrasound during common carotid artery compression as an accurate method of predicting the collateral hemispheric pressure as validated by back-pressure measurements at carotid endarterectomy.[3] Either technique is important in defining the potential collateral around an extracranial carotid artery lesion, a matter of particular importance in patients being observed who have asymptomatic carotid artery disease.

The authors suggest that patients with documented internal carotid artery occlusion should be considered candidates for an extracranial bypass procedure. Although neurosurgical advances have made this operation relatively safe and effective, I am unconvinced that this procedure is necessary for most patients with internal carotid artery occlusion. The natural history of internal carotid artery occlusion is generally favorable.[4] Extracranial-intracranial bypass procedure is reserved for patients in whom recurrent transient ischemic attacks develop after proved internal carotid artery occlusion and only after assuring that microemboli are not emanating via the external carotid artery from a lesion at its origin or the blind stump of the internal carotid artery.

Although the authors have emphasized the important role of sensitive direct carotid artery noninvasive screening in the postoperative period, I find the 15% incidence of reported recurrent stenosis higher than that in my own practice. In a follow-up of 115 cases of carotid endarterectomies over five years, the late incidence of recurrence detected by routine direct carotid artery Doppler examination with sound spectrum analysis was less than 5%. Whether this relatively low incidence is related to intraoperative detection and correction of residual technical defects using Doppler ultrasound or the routine use of antiplatelet agents postoperatively is difficult to determine. Nevertheless, I agree that careful preoperative, intraoperative and postoperative noninvasive evaluations are necessary to identify carotid artery lesions that are usually asymptomatic and unrecognized by patients and physicians alike.

Finally, I would strongly support the authors' approach to the integrated use of noninvasive diagnostic technology with selected use of intravenous versus intraarterial angiography in patients with suspected cerebrovascular disease. Indeed, the advent of digital subtraction angiography has not and should not replace noninvasive diagnostic techniques. To the contrary, this new radiologic technology has made the noninvasive laboratory all the more important in screening patients with symptoms of cerebral ischemia as well as asymptomatic patients or those with atypical, nonlateralizing symptoms. I agree with the authors that patients with symptoms who have noninvasive evidence of significant extracranial carotid artery atherosclerosis may benefit from intravenous digital subtraction angiography. I personally will operate on such patients based on the findings on an intravenous arteriogram when a significant carotid artery lesion is visualized and in agreement with the findings of the noninvasive laboratory. It has been my experience, however, that patients with normal noninvasive studies have rarely shown a lesion on intravenous angiography, but intraarterial angiography may occasionally record an ulcerated plaque amenable to operation. I thus recommend proceeding directly to intraarterial imaging if the noninvasive study shows no abnormalities.

For asymptomatic patients, controversy persists regarding the best form of treatment. I would generally agree with the authors' approach, although a prospective study using noninvasive techniques is under way to define the natural history of detected asymptomatic carotid artery disease in a large multicenter family practice study supported by the National Heart, Lung and Blood Institute. Those studies are only possible with the advent of newer noninvasive diagnostic technology. Such epidemiologic information, coupled with the significant advances reviewed so well by Bandyk and Thiele, will greatly aid physicians in providing cost-effective diagnosis and treatment of patients with cerebrovascular disease.

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Improving Psychiatric Care for Elderly Patients

DR GOODWIN'S PRESENTATION elsewhere in this issue, "Common Psychiatric Disorders in Elderly Persons," is comprehensive, timely and informative, not only to psychiatrists but to a broad range of medical specialists. The majority of the elderly who experience age-related emotional disturbances are initially treated by physicians in specialties other than psychiatry—primarily internal medicine, family practice and general practice. Treatment by them, in most situations, suffices and relatively few are referred for psychiatric care. This is appropriate in that elderly patients often have emotional disturbances associated with physical illnesses or senescent decline, and appropriate treatment of an associated illness frequently serves to ameliorate the emotional distress.

Dr Goodwin has very appropriately commented that psychiatry is less disposed to ignore the elderly than it once was. The rapidly increasing numbers of senior citizens among us, and their impact on the health care

delivery system, have been reflected in the establishment of a National Institute on Aging and the increasing number of journals relating to issues of aging.

Until about 15 years ago, a state mental hospital was the treatment setting for most emotionally disturbed elderly persons. They were very underrepresented, proportionally, in psychiatric outpatient clinics and this continues to be true. In addition, they are less likely to receive treatment that is equivalent in duration or type of intervention to that younger persons receive. In recent years, however, there has been an increasing awareness that, as a group, they need not be considered separately from patients of other ages in terms of appropriateness for the range of treatment approaches.

It is especially important that services delivered by the various medical specialties be coordinated in the care of elderly patients. In a study of the use by elderly persons of psychiatric emergency services,[1] it was noted that they often have significant psychiatric and other medical disorders and that they tend to return frequently to emergency services. The need for repeated visits was considered to be, in part, a function of the need for better teamwork among the specialties involved. It has also been reported that 30% of the psychiatric referrals in a general hospital setting relate to medical and surgical patients 65 years or older, largely for delirium, depressive and anxiety disorders and dementia,[2] and Goodstein[3] has called attention to the multidimensional clinical aspects of cerebrovascular accidents in elderly persons because of such problems as disfigurement, difficulties in communication and emotional sequelae.

A number of widely held beliefs, when subjected to closer scrutiny, raise serious questions about current practice associated with these beliefs. There is a prevailing opinion about the presence of depression during the early stages of cognitive decline in cases of Alzheimer's disease. A comparison of samples of 30 patients with early Alzheimer's disease and an equal number of matched controls on two occasions one year apart did not show significantly different degrees of depression between the two groups.[4] This raises the question of whether, when both are present, the depression may represent an independent disorder. Meyers and Mei-Tal,[5] in their study of 43 patients older than 60 years and with a median age greater than 70 years, reported a lower incidence of complications with tricyclic antidepressant medication than anticipated from previous reports. It was their conclusion that, though the elderly were more prone to central anticholinergic syndrome than younger patients, the incidence of side effects was less than commonly believed and that factors other than the tricyclic medication alone may have contributed to prior findings of greater risk.

The issue of potential renal impairment with lithium use by the elderly is of continuing interest. Using serum creatinine concentration as the index of glomerular filtration rate in a controlled group of normal subjects, Decina and co-workers[6] reported that there is a small decrease in filtration that they did not consider to be of clinical significance. They suggested that other factors that influence filtration, which were not controlled in prior studies, may have influenced other reports to the contrary. In addition, Bushey and associates[7] studied 15 elderly patients over time in nursing homes, where the average duration of lithium treatment was five years. The use of lithium was found to be relatively safe and useful and severe renal impairment was not found. Bradycardia and ectopy were found, however, in 20% of these patients, but it was noted that it was difficult to conclude which of other medications may have been causative or contributory. Jefferson's article on the use of lithium in elderly patients may be of general interest in view of the increasing use of lithium in this age group.[8]

Elderly persons present special problems in differential diagnosis and treatment. They constitute probably the most diverse segment of the population psychosocially and biologically, as well as in their response to drugs, which often results in diagnostic challenge wherein symptoms may be confusing in their range and complexity. Furthermore, age-related dementing cognitive disturbances must be differentiated from functional disturbances and a range of other organic causes. Reisberg and colleagues[9] recommend the routine use of a rating scale that has been validated with neuropathologic findings, both as to the presence of degenerative dementia and the ability to assess the stages of degeneration.

Whereas in the past the elderly have received either total care in psychiatric settings or scarcely any at all, increasing attention now is being paid to outpatient psychotherapeutic treatment for this age group. They present themselves with the entire range of neurotic and psychotic syndromes, either of their own volition or because their behavior has become disturbing to others. Their disturbances may be specific to the aging process, exacerbations of prior episodes or functions of previously latent tendencies, and may, in part, be functions of the status given by our society to the elderly. Psychotherapy is considered indicated for a broad range of these persons. Many of them present, individually or in combination, a change in functioning of the central nervous system, as well as a functional disturbance. Special attention, however, is indicated for such age-related developmental tasks as acceptance of changes in the egress of drives, of increasing slowness in the manipulation of memory, of coping with losses, of bodily changes and, for some, the resolution of one's own death.[10]

It is apparent that psychiatry must reconsider its priorities so as to include more significant treatment services to the elderly. This is a confrontation, as well as an opportunity, that must be met.

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Physicians on School Boards

IT IS NOT UNCOMMON for physicians to serve on school boards and in doing so they make a major contribution to the communities in which they live and practice. This kind of community service is of special significance at this time when there is reason to believe that our primary and secondary schools are very much in need of strengthening in many ways. It is no secret that students are entering our colleges and universities with less than adequate basic training, particularly in mathematics and science. In fact this has now become a matter of notable national concern. It is well known that these are among the disciplines that teach one to think basically, and clearly. There are many reasons for this pedagogic weakness, not the least of which is that persons who are adequately prepared to teach these subjects can usually find work that pays them much more money in business or industry simply because they possess skills in these subjects. But whatever the reasons there has developed a critical shortage of good teaching in mathematics and science in many school districts, and this can only put students at a disadvantage when one considers the importance of a basic knowledge of mathematics and science to a higher education, or for an understanding of today's world, or for their future economic well-being in the postindustrial society in which they will live and work.

Physicians can speak authoritatively on the need for a basic understanding of mathematics and science and the need for laying the basic groundwork during the school years. Physicians who serve on school boards are obviously in a position to play an important role, but physicians as parents and educated citizens in the community can also bring their influence to bear. The issue is an important one and one that can only have its effect on the future of health care as well. Whether serving on a school board or not, physicians should do what they can to help with this problem which must always be a local as well as a national one. MSMW

Case Reports

Pitfalls and Perils of Intravenous Lidocaine

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INTRAVENOUS LIDOCAINE has been used widely over the past 30 years, primarily in the setting of ventricular fibrillation and ventricular tachycardia. It is estimated that ventricular fibrillation will develop in 3% to 10% of patients with uncomplicated acute myocardial infarction.[1] For many years certain designated "warning dysrhythmias" were believed to be accurate indicators of the likelihood of malignant ventricular dysrhythmias. However, in 25% to 50% of patients with acute myocardial infarctions in whom ventricular fibrillation develops there will be no "warning dysrhythmias," generally defined by (1) premature ventricular contractions more than six per minute, (2) "R-on-T" phenomenon (the R wave of the premature ventricular beat is close to the T wave), (3) multifocal premature ventricular contractions and (4) runs of ventricular tachycardia. In several studies the incidence of warning dysrhythmias was found to be the same in patients in whom ventricular fibrillation develops and in those in whom it does not.[2] Even when these warning dysrhythmias are present, over 50% may be overlooked by intensive care staff.[3]

In more than 90% of patients with acute myocardial infarctions in whom ventricular fibrillation occurs, it will do so within 12 hours after their initial symptoms.[4] A number of authors now advocate the use of prophylactic lidocaine during the first 24 hours following the suspected infarction in both the intensive care and prehospital settings.[10] Because of the frequent occurrence of side effects of intravenous lidocaine, its use following acute myocardial infarction is not universally accepted in practice. We recently treated a case of iatrogenic occult lidocaine overdose that prompted further review of similar cases as well as a review of the types of toxic responses reported from intravenous use of the drug.

Refer to: Bryant CA, Hoffman JR, Nichter LS: Pitfalls and perils of intravenous lidocaine. West J Med 1983 Oct; 139:528-530.

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Report of a Case

A 71-year-old woman came to the Emergency Medicine Center, University of California, Los Angeles, complaining of five days of substernal chest pressure radiating to her left upper arm and teeth. It was, however, absent at the time of presentation. She said she had had no history of heart disease, myocardial infarction or neurological disease. She had been told by her private physician 20 years before that she had "bundle branch block." Past medical history was negative for hypertension, diabetes, cancer or tuberculosis.

On initial examination the patient was pleasant and in no acute distress. Presenting vital signs were as follows: blood pressure 146/98 mm of mercury, heart rate 108 per minute, respiration rate 20 per minute and temperature 36°C (96.8°F). The remainder of her physical examination was unremarkable. An electrocardiogram showed an intraventricular conduction defect with left axis deviation and clockwise rotation, and a probable old anterior myocardial infarction.

At this time the examining physician left to attend another patient, but before leaving requested the nurse start an intravenous infusion of 5% dextrose in water at a keep-open rate. Administration of nasal oxygen was continued and the patient kept in a monitored bed. When the physician returned 45 minutes later, the patient was cool, diaphoretic and unresponsive to painful stimuli. Her heart rate was 95 per minute, and her systolic blood pressure was 120 mm of mercury. Her neurologic examination now showed rare clonic movements, with a positive Babinski reflex on the right. A chest x-ray film was clear and electrocardiographic findings were unchanged. Arterial blood gases, electrolytes, complete blood count, glucose and blood urea nitrogen were all within normal limits. At this time one of the nurses noted that the 500 ml solution that the patient was receiving intravenously had the following handwritten notation on the bag: "Lido 2 gm/500cc." A total of 450 ml of this solution had been infused in the previous 45 minutes. The infusion was immediately stopped, and during the next 20 minutes the patient became alert and oriented to person, place and time. It was estimated that she had received approximately 1,800 mg of lidocaine in a period of approximately 45 minutes. The patient was subsequently admitted to the coronary care unit with the notation "rule out myocardial infarction." She was discharged after an uneventful hospital course four days later, without evidence of acute myocardial infarction. No further ill effects of lidocaine were noted. Specimens from the intravenous solution she had received and from the patient's serum were sent for lidocaine level determinations but unfortunately were lost.

Discussion

The biphasic pattern of distribution of lidocaine necessitates a dosage regimen of one or two initial intravenous boluses followed by an intravenous drip. One effective method of lidocaine administration would be as follows:

- Initial bolus of 75 to 100 mg or approximately 1.0 to 1.4 mg per kg of body weight.
- Second bolus ten minutes later of 50 mg, or approximately 0.7 mg per kg.
- Infusion of 2 to 3 mg per minute, or about 20 to 50 μg per kg per minute.

Standard dosage regimens must be modified in patients whose disease states change either the ability of the liver to clear lidocaine or the drug's volume of distribution. In general when there is hepatic dysfunction or decreased hepatic blood flow the infusion rate must be reduced. A decrease in blood volume necessitates a decrease in the initial bolus of lidocaine. In chronic liver disease standard bolus dosages are unchanged, but the infusion rate should be reduced to half the standard rate. Patients with congestive heart failure have both a decrease in volume of distribution and decreased hepatic blood flow resulting in decreased hepatic metabolism. These patients should thus be given half the standard loading dose as well as half the standard infusion rate of lidocaine. Patients with uncomplicated acute myocardial infarction and renal failure should receive standard doses of lidocaine.[6]

The pharmacokinetics of intravenous lidocaine that has been infused for longer than 24 hours may not always be identical to infusions of shorter duration (less than 12 hours). LeLorier has shown a mean half-life of the elimination phase of 3.2 hours for infusions of greater than 24 hours as opposed to the 1.5 hours determined for infusions of less than 12 hours. Significant toxic responses can result if this increased half-life is not anticipated.[7] Deglin advocates the use of rapid enzyme immunoassay technique for the determination of serum lidocaine levels. He found 51% of patients receiving lidocaine infusions in the coronary care unit were within the therapeutic range; 30% were above the therapeutic range, and 19% were below therapeutic levels. He emphasizes that toxic responses to the drug may be difficult to recognize in a patient with complex and multiple medical problems.[8]

Adverse Effects of Lidocaine

Minimum lidocaine levels effective in suppressing ventricular arrhythmias range between 1.4 and 2.0 μg per ml. Signs of toxic responses are first seen with levels of 5 to 6 μg per ml, and there is good correlation between serum levels and the response. The most common side effects of high doses of lidocaine are on the central nervous system and may consist of paresthesias, confusion, dizziness and respiratory depression, progressing to psychosis, loss of consciousness and seizures. These signs are completely and rapidly reversible when lidocaine administration is discontinued.[9] In Pfiefer's study of 750 patients receiving lidocaine for treatment of cardiac arrhythmias, it was found that 6.3% had adverse reactions, most of which were central nervous system related. In 1.6% of cases the attending physician judged the adverse reaction to be "life-threatening."[10]

Conduction defects have also been reported with the use of intravenous lidocaine and are more frequent when preexisting bundle branch blocks are present.[11,12] Lidocaine has little effect on the normal sinoatrial node but can produce profound bradycardia in the patient with sick sinus syndrome.[13-15] This suppressive effect on the sinoatrial node may be accentuated by digitalis, quinidine, phenytoin or amiodarone.[16-19]

Sinus standstill has been reported with lidocaine administration even when the sinoatrial node was normal and without evidence of toxicity from other drugs. Cheng reported such a case; however, his patient had congestive heart failure and received 200 mg of lidocaine over five minutes.[14] More recently, Antonelli reported sinus standstill in a patient after an acute myocardial infarction and suggested that ischemia of the sinoatrial node may make it more susceptible to the inhibitory effect of lidocaine.[20] In general, in the absence of ischemia, sinoatrial node-suppressive drugs or congestive heart failure, true depression of the sinoatrial node is extremely rare but has been reported.[13]

The atrioventricular node in an ischemic heart may be similarly more susceptible to suppression by lidocaine.[21] Kuo noted that patients with complete atrioventricular block and acute myocardial infarction have severe bradycardia or asystole when given lidocaine while patients without infarction but with block had no such effects. Prophylactic pacemaker insertion in patients with acute myocardial infarction and complete atrioventricular block should be done before lidocaine administration.[22] Intravenous lidocaine may also induce high grade exit block in patients with complete atrioventricular block located distal to the His bundle.[23]

Patients who have received subcutaneous lidocaine for local pacemaker insertion have been shown to have blood levels of lidocaine in the therapeutic range.[24] Kosowsky has shown increased ventricular escape intervals in patients with complete heart block who received subcutaneous lidocaine and had therapeutic blood levels. It is possible that subcutaneous lidocaine is directly related to episodes of asystole seen during pacemaker implantation.[25]

A decrease in the inotropic state of the heart is an occasional side effect of lidocaine, and may be particularly detrimental to patients in congestive heart failure. In Pfiefer's study cited earlier, adverse reactions to lidocaine were seen significantly more frequently in patients with congestive heart failure and acute myocardial infarction, and in those patients who died of their disease.[10]

Toxic levels of lidocaine may result when it is given concurrently with cimetidine. Splanchnic circulation is decreased by cimetidine resulting in decreased hepatic blood flow. In the presence of cimetidine the rate of

lidocaine's metabolism is thus reduced. When cimetidine and lidocaine are administered together lidocaine dosage must be reduced and lidocaine levels should be checked frequently to prevent toxic reactions.[26]

There have been five case reports of lidocaine overdose in which a 800- to 2,000-mg intravenous bolus of lidocaine was mistakenly injected when a much lower dose was ordered.[27-31] In three cases, there was confusion concerning the two types of prepackaged syringes (100 mg and 1,000 to 2,000 mg). In all five patients convulsions occurred, and ultimately cardiopulmonary arrest. Three patients survived (one who received a 800-mg intravenous bolus, one who received 1,000 mg and the other a full 2,000-mg bolus).

In two other cases excessively high drip rates of lidocaine have been reported to cause toxic reactions.[32,33] In one case an extremely rapid infusion resulted when the wrong intravenous line was opened for a fluid challenge. This patient received 600 mg of lidocaine in ten minutes.[32] In the second case, the drip was mixed incorrectly and the patient received 400 mg in 30 minutes.[33] In only one of these patients did hypotension occur but both had signs of central nervous system toxicity.

In our case of toxic response to lidocaine several mistakes were made. First, there was poor and improper labeling of a solution of 5% dextrose in water mixed with 2 grams of lidocaine. Second, when this solution was not used on an earlier patient it should have been discarded rather than replaced on a shelf designed for 5% dextrose in water storage. Finally, our "TKO" (to keep open) rate was much too fast and resulted in the patient receiving more than 450 ml of fluid in 45 minutes. These combined mistakes led to what seemed at first to be a mysterious change in our patient's mental status, followed by the development of seizure activity and a mild fall in blood pressure.

Our patient probably received more than 1,800 mg of lidocaine in 45 minutes. Signs of a toxic reaction would most likely have occurred by ten minutes, when she had received 300 mg of lidocaine. It is interesting that our patient did not have major changes in blood pressure, nor were her underlying conduction abnormalities accentuated. Manifestations of toxicity in our patient were limited primarily to the central nervous system, and were completely and rapidly reversed with termination of the infusion.

Therapy

The therapy of lidocaine overdose is primarily supportive. Bradycardia may be reversed with atropine by increasing conduction through the atrioventricular node.[13] Isoproterenol should be given to increase the heart rate in cases where atropine is unsuccessful and the patient has signs of shock. Hypotension in itself can be treated with volume loading, Trendelenburg position, vasopressors or the military antishock trousers (MAST suit). Vasopressors such as dopamine may help to sustain blood pressure until lidocaine is cleared. Complete heart block, sinus arrest and ventricular asystole may require temporary pacing until toxic levels of lidocaine have been eliminated and normal conduction resumes.[12,14,20,28]

As prophylactic lidocaine use increases, so will the incidence of its untoward and toxic reactions. Conspicuous labeling of prepackaged syringes and rigid observation of all intravenous drips will diminish the incidence of lidocaine overdose. Knowledge of adverse effects together with careful observation and monitoring of all patients receiving lidocaine is crucial to early detection of adverse reactions to lidocaine.

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Inflammatory Crystallosis

IgA Gammopathy, Polyserositis and Extensive Fibrosis Associated With Intracellular Crystalline Protein Deposits

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WE PRESENT the case of a man with a plasma cell dyscrasia and widespread proteinaceous crystal deposition in phagocytic cells. These deposits were associated with extensive inflammation and fibrosis that gradually led to his death. This case is remarkable for the abundance of crystal deposition, and apparently unique because the distribution of the crystals appears to explain the clinical course of events.

Report of a Case

A 60-year-old man, a retired sheet-metal and insulation contractor, saw his physician in 1976 because of abdominal pain. After unrevealing clinical evaluation, a laparotomy was carried out and showed thickened peritoneum, adhesions and a chronic inflammatory mass at the hepatic flexure. Some crystals were seen within mononuclear cells in the specimen. After careful examination, no neoplasm, asbestos bodies or infectious agents were identified. He was taking no medications during this time.

Six months later the patient had lost 13.6 kg (30 lb) and the abdominal pain had returned. Evaluation then showed anemia and hypoalbuminemia. Skin testing showed anergy to six reagents, including purified protein derivative. Protein electrophoresis showed slight increases in α-1 and α-2 and moderate increase of β to 1.8 mg per dl. A fluorescent antinuclear antibody test was positive at 1/20, speckled. Coombs' tests were negative. Latex fixation was negative. A liver and spleen scan showed hepatomegaly. No abnormalities were found on abdominal and selective visceral arteriography. In December 1976 a second diagnostic laparotomy showed ascites and granulomatous mesenteric adenitis. Liver biopsy showed mild nonspecific triaditis. Bone marrow biopsy showed increased myeloid elements with normal maturation and increased plasma cells (3% to 4%). Ascitic fluid studies showed a sterile exudate. Subsequent cultures of fluid and lymph nodes were negative for fungi and tuberculosis.

In February 1977 the patient was readmitted for failure to gain weight and continued abdominal pain. He had lost 4.5 kg (10 lb) more and had new bilateral pleural effusions. Hepatomegaly, anemia and skin test anergy persisted. His pleural fluid had small numbers of mononuclear cells and a protein concentration of 3.6 mg per dl. Total serum protein was 6.0 and albumin was 2.8 mg per dl. Pleural biopsy gave inadequate tissue. Multiple radiologic studies were nondiagnostic and a third exploratory laparotomy was done. An intraoperative pancreatogram showed no abnormalities. Mesenteric and omental biopsy specimens showed dense serosal fibrosis. Because of severe dysphagia, a jejunostomy was carried out for feeding, and prednisone therapy was started at 30 mg per day given by mouth. Later in 1977 the prednisone dosage was tapered to 10 mg per day. That autumn, he had two episodes of partial small bowel obstruction, relieved after nasogastric suction and enemas.

From 1977 to 1980 the patient lived at home on a regimen of oral and jejunal feedings. In March 1980 he was readmitted with pericarditis and recurrent pleural effusions. The latter were drained, showing exudates with mostly mononuclear cells. Symptoms resolved with indomethacin therapy. Serum protein electrophoresis showed values for total protein of 7.6, albumin of 3.4, α-1 of 0.4, α-2 of 0.97, β of 2.09 and γ of 9.72 mg per dl. Immunoelectrophoresis showed a κ-reacting monoclonal IgA. Total IgA was 2,210 mg per dl. Pulmonary function tests showed a restrictive pattern with a vital capacity of 1.25 liters (30% predicted) and an FEV_1 (forced expiratory volume in one second) of 1.2 liters.

In May 1980 he had two episodes of aspiration. Aperistalsis of the esophagus was demonstrated, with aspiration of barium. Hepatomegaly and new jugular venous distension were noted. Nasogastric feedings led to more aspiration, so a gastrostomy was done. Prednisone administration was continued at 10 mg per day and no other medicines were instituted.

In June 1980 he was readmitted with cachexia. Respirations were 24 per minute and pulse was 90. Rales, jugular venous distension and a summation gallop were present. There was no adenopathy and his hepatomegaly was unchanged from prior admissions. Hematocrit was 39%, leukocyte count was 10,000 per μl with 95 polymorphonuclear leukocytes and 4 band cells; platelets appeared normal. Results of electrolyte, renal, hepatic function and coagulation tests were unremarkable. The CH_{50} was 675 units (normal 800 to 1,650), the C3 was 48 (normal 90 to 120) and the C4 was 22 mg per dl (normal 11 to 75). Urine immunoelectrophoresis showed a trace of κ-reacting Bence-Jones proteins. The result of a Raji cell assay for immune complexes was 54 μg AHG (aggregated human gonadotropin) Eq per ml of serum (normal, less than 12). An x-ray film of the chest showed a widened cardiac silhouette and 1.2 cm of pleural thickening

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bilaterally. All radiographs showed osteoporosis, but no focal lesions were seen.

Repeat bone marrow biopsy showed slight plasmacytosis (3% to 4%) without confluence of cells or nuclear atypia. Intracellular crystals were seen in most phagocytic cells. Review of all previous biopsy specimens showed similar crystals, which on special stains appeared to be widespread, proteinaceous and located chiefly within macrophages. The hypothesis of a lymphoproliferative disorder producing a crystalline paraprotein with inflammatory properties was formulated and chemotherapy was initiated.

The hospital course was complicated by recurrent aspiration of oral secretions, pneumonitis and gastrointestinal bleeding. Antibiotic and diuretic therapy was started along with parenteral nutrition and transfusions. Chronic respiratory insufficiency developed, refractory to aggressive diuresis and pulmonary toilet. Renewed intestinal bleeding and worsening respiratory failure developed during the first cycle of cyclophosphamide, vincristine and prednisone. In agreement with the patient's and family's wishes, resuscitation was not attempted after the patient suffered a respiratory arrest.

Findings at Autopsy

An exuberant overgrowth of fibrous tissue obliterated the pleural, pericardial and peritoneal cavities. The retroperitoneal, mediastinal and cervical soft tissues were involved extensively as well. Some areas of fibrosis were quite dense and cell poor, while other areas were vascular, edematous and infiltrated by lymphocytes, plasma cells, neutrophils, eosinophils and macrophages. Other major findings were pulmonary edema, focal interstitial pneumonitis, mild cardiac hypertrophy with focal fibrosis, hepatic centrilobular congestion with necrosis, acute pancreatitis, osteoporosis and cachexia. Bone marrow samples showed moderate plasmacytosis as seen on antemortem biopsy specimens, but nowhere was there a confluence of cells or nuclear dystrophy indicative of a neoplasm. Using appropriate stains, no asbestos bodies, tubercle bacilli or fungi could be found.

Crystalline deposits were seen in neutrophils and macrophages of all inflammatory tissues (Figure 1). Similar crystals were found in marrow, splenic and hepatic macrophages (Figure 2), in renal tubular lumens and glomerular endothelial cells and focally within the fibrous interstitium of the heart, lungs, kid-

Figure 1.—Adhesions between pericardium and visceral pleura. Note cellular fibrous tissue with inflammatory cells. Arrows indicate densely stained intracellular crystals. (Modified Brown-Brenn stain, reduced from ×700.)

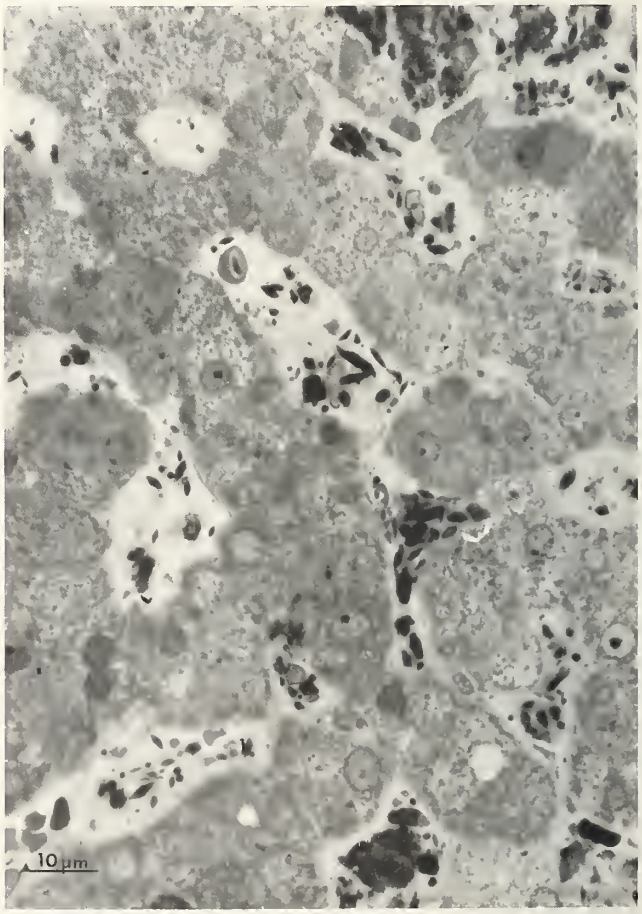

Figure 2.—Liver biopsy, epoxy section. Note crystals in Kupffer's cells. (Toluidine blue stain, reduced from ×700.)

neys, prostate and testes. The crystals also were abundant in the parenchymal cells of the posterior pituitary gland and the adrenal cortex.

Review of sections from all premortem biopsy specimens between 1976 and death showed the crystals in all samples of bone marrow, liver and mesenteric tissues. They appear to be an integral part of the necrotizing granulomas seen on the 1977 samples, being demonstrable readily within the cytoplasm of Langhans' cells.

The crystals were faintly eosinophilic, not acid-fast, and both Congo red and periodic acid-Schiff negative. They were azurophilic in smears with Romanovsky's stain and strongly fuchsinophilic. The Brown-Brenn stain (for bacteria in paraffin sections) gave a dramatic demonstration of the prevalence of the crystals (Figure 1). This staining pattern is typical for proteins.

The crystals remained unstained by immunochemical means, despite the use of antibodies to IgA, IgG, IgM, κ and λ light chains, J chains and secretory product. This was true despite use of fresh frozen or fixed paraffin sections, with or without prior partial trypsin digestion, and with indirect immunofluorescence or immunoperoxidase methods. In the bone marrow, plasmacytes showed a slight increase in the percentage of IgA positive cells, but a heterogeneous pattern of κ and λ reactivity.

With electron microscopy, crystals were seen chiefly in macrophages and Kupffer's cells, less often in granulocytes and infrequently in plasma cells. Crystals were 0.9 to 15 μm in maximum dimension, often of rhomboid shape with sharp margins, and were bounded by a unit membrane like that of a lysosome. The interior of the crystals had a fine granular matrix, and in some a clearly discernible substructure of parallel lines could be seen (Figure 3). Structural analysis was carried out on an electron microscope fitted with a goniometer stage tilted until two crystal axes were apparent (insert, Figure 3). Fourier transformation of the digitized image was used to analyze its diffraction pattern, showing a cubic lattice structure with a unit cube side dimension of 55 nm. Further analysis of the crystals has not been possible so far.

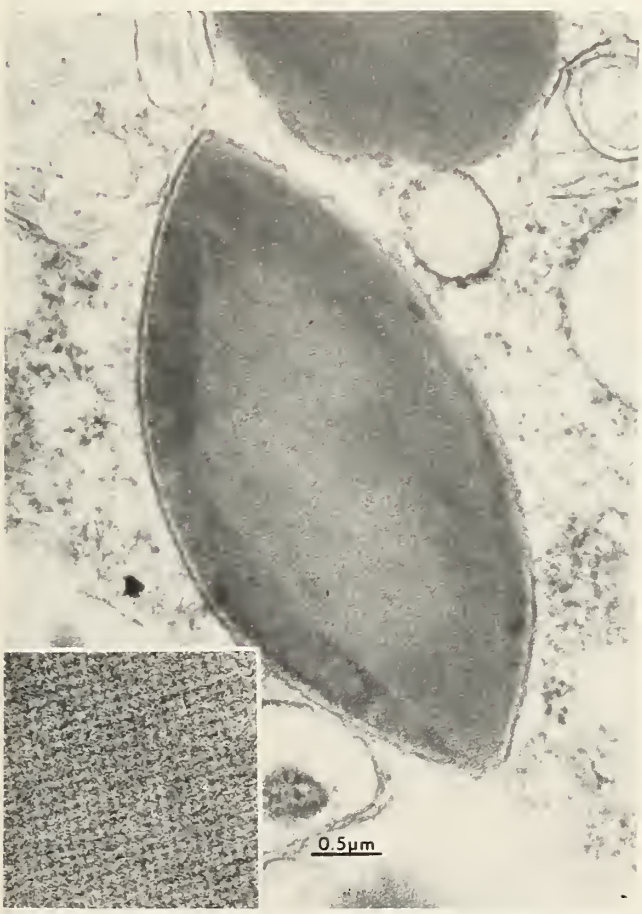

Figure 3.—Liver biopsy specimen with typical crystal in Kupffer's cell. Note surrounding unit membrane and lamellar internal structure of crystal. Electron micrography (×12,500). Insert: electron diffraction image (×33,000).

Comments and Discussion

To summarize, the patient had progressive polyserositis of unknown cause, leading to widespread massive fibrosis with restrictive pleural and pericardial disease. Biopsy and autopsy studies showed widespread deposition of proteinaceous crystals in the reticuloendothelial system, marrow and all areas of fibrosis, including the serosal surfaces. Although an IgA-κ-reacting light chain was present in the serum, we were unable to find any immunochemical staining in the crystals or clear evidence of a monoclonal plasma cell proliferation.

Intracellular crystalline deposits have been reported in myeloma and in B-cell neoplasms. The latter are usually in cases of patients with typical chronic lymphocytic leukemia who have crystals described incidentally in a subpopulation of their blood lymphocytes.[1-8] Crystals have also been shown in the plasma cells of Waldenstrom's macroglobulinemia,[9] multiple myeloma,[9,10] gastric plasmacytoma[11] and other cases of less aggressive plasma cell dyscrasias.[12,13] Finally, Mullen and Chalvardjian[14] described a patient with bulky myeloma and hyperviscosity. He had widespread deposition of crystals with a rhomboid shape and staining characteristics very similar to the current case. Their crystals had no internal periodicity when viewed with an electron microscope, and did not react with immunochemical reagents. In all the above cases, the clinical course of the patients involved did not appear to correlate with the presence of tissue or intracellular crystals.

Polyserositis has been a feature of many different disease processes. Our patient's clinical course, physical findings and laboratory and pathologic data do not support diagnoses of lupus, other collagen vascular disorders, vasculitis, angioimmunoblastic lymphadenopathy or sarcoidosis. Infectious causes were considered and none were found, despite extensive and repeated biopsy and culture. Industrial exposures, particularly

to asbestos, could not be supported pathologically, nor could a diagnosis of retroperitoneal fibrosis.

The staining characteristics of the crystals and their appearance on electron microscopy suggest that they are protein aggregates with little or no polysaccharide. The lack of reaction with antibody reagents is puzzling, and there are several possible explanations. It is possible that the crystalline array may have shielded antigenic sites, preventing binding of our reagents. Since the presence of immune complexes was suggested by a Raji cell assay, the appropriate binding sites for our reagents may already be occupied in the complexes, which then crystallized and were engulfed by phagocytic cells. Another alternative is that the crystal protein may be an incomplete immunoglobulin or light chain without fully developed binding sites for our reagents. This might be due to defective glycosylation of the paraprotein, or alteration of its structure during secretion from the cells of origin.[15,16] Finally, the protein in the crystals may not be a component of immunoglobulin at all. However, we favor the hypothesis that the crystals are some form of immunoglobulin paraprotein.

The role of the crystals in the pathogenesis of the inflammatory response is obscure. They may be resistant to phagocytic digestion, leading to eventual cellular engorgement, rupture and release of inflammatory mediators. This would be analogous to the effect of gouty crystals or asbestos bodies on neutrophils. Alternatively, crystalline protein deposition may be a consequence of this patient's inflammatory response, rather than a cause. Unfortunately, our histochemical and electron microscopic studies do not further our insight into these possibilities.

In conclusion, we have described the combination of an IgA gammopathy, polyserositis and progressive massive fibrosis, associated with widespread deposition of intracellular protein crystal in all areas of inflammation. We suggest that this is a very unusual consequence of a plasma cell dyscrasia, an inflammatory crystallosis.

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Cardiac Presentation of a Bronchogenic Cyst

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Bronchogenic cysts are congenital malformations usually identified in infants and children because of pulmonary infection or respiratory compromise.[1,2] In adults, clinical manifestations are infrequent and the cysts are part of the differential diagnosis of mediastinal tumors.[3] The patient in this report presented with cardiovascular findings, suggestive of mitral stenosis, caused by a bronchogenic cyst.

Report of a Case

An asymptomatic 24-year-old woman, a medical technician, was a control subject for a new electrocardiographic machine in her hospital and a question of an abnormality was raised. Subsequent review showed a normal tracing. She was unaware of a heart murmur since childhood. On examination, findings included an accentuated S_1, a grade 2/6 systolic murmur at the left sternal border and an early grade 2/4 diastolic rumble at the apex which was louder after exercise.

On an x-ray film of the chest, heart size was normal and the lung fields were clear but a mass posterior and superior to the left atrium elevated and compressed the left mainstem bronchus. A fine rim of calcium was present at the margins of the mass (Figure 1). M-mode and two-dimensional echocardiography showed a normal mitral valve. In the region of the left atrium, a mass with an echodense rim was identified but it was unclear whether it was intraatrial or extraatrial in location (Figure 2).

On cardiac catheterization, rest and exercise pressures and flows were within normal limits. Results of a left ventriculogram were normal. On the pulmonary venous phase of a pulmonary artery injection, the

Refer to: Reinhart SE, Miller R, Mayer W, et al: Cardiac presentation of a bronchogenic cyst. West J Med 1983 Oct; 139:534-536.

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posterior-superior aspect of the left atrium appeared compressed with splaying of the pulmonary veins. A computed tomogram of the chest showed a 7-cm spherical mass with a fine rim of calcium between the left atrium and left mainstem bronchus distorting both structures (Figure 3).

With a preoperative diagnosis of a bronchogenic cyst, right thoracotomy was carried out. A cystic structure connected to the left mainstem bronchus with fibrous attachments to the pericardium and esophagus was identified and removed. Pathologic evaluation confirmed the diagnosis of a bronchogenic cyst. The cyst wall was speckled with small areas of calcium and was lined with pseudostratified epithelium with goblet cells and cilia. The postoperative course was benign. A 1/4 apical diastolic rumble was heard postoperatively.

Discussion

Initial concern for a severe cardiac abnormality such as mitral valve stenosis, a left atrial mass (such as

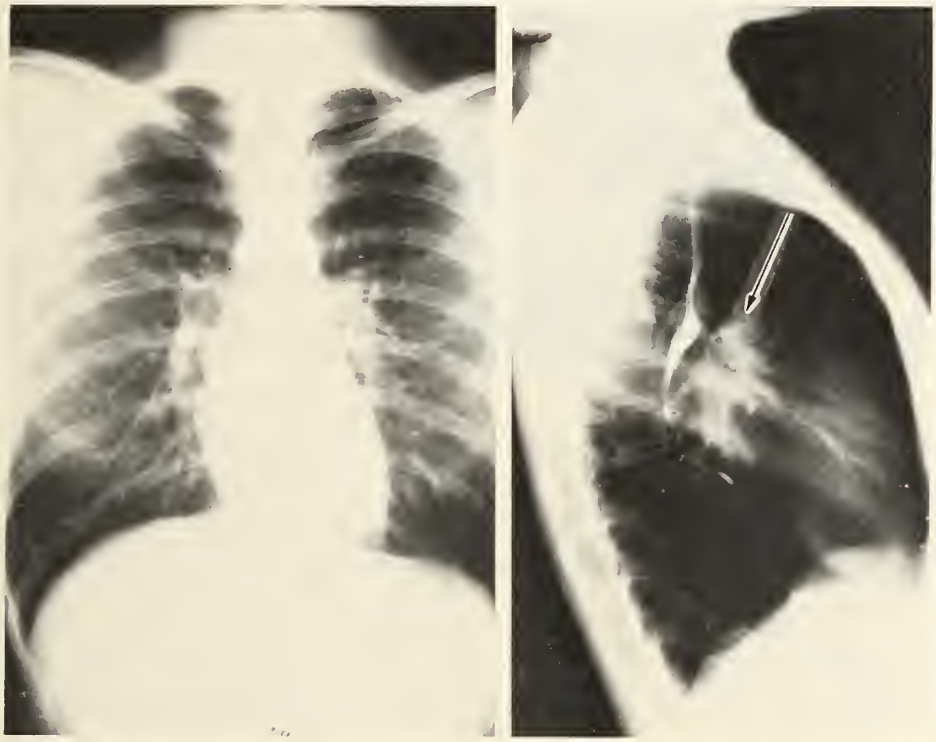

Figure 1.—Posteroanterior and lateral x-ray film of the chest showing a spherical mass behind and above the left atrium distorting the left mainstem bronchus. There is also a fine rim of calcium seen at the margins of the mass (arrow).

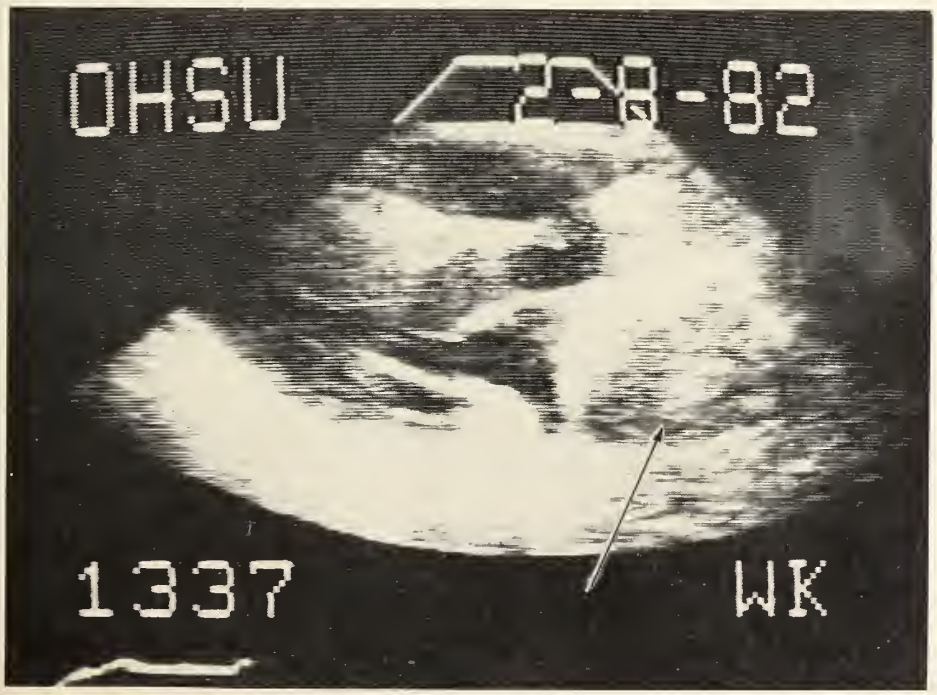

Figure 2.—Two-dimensional echocardiogram in the parasternal long axis view showing the distortion of the left atrium by the cyst and the suggestion of a left atrial mass (arrow).

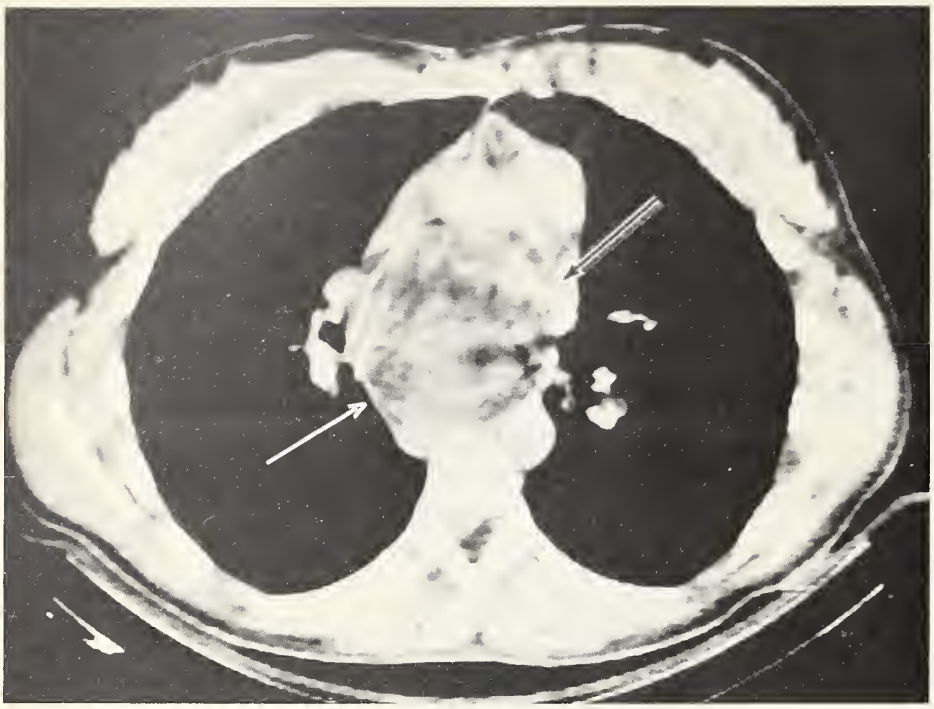

Figure 3.—Computed tomogram showing a spherical cyst with a rim of calcium displacing the left atrium. The cyst is outlined by arrows with the heart displaced anteriorly.

myxoma or teratoma), or a left atrial partition (cor triatriatum) in this young woman based on examination and chest x-ray findings was allayed by eventual definition of a benign extracardiac cyst. Symptomatic patients usually present with pulmonary complaints[3-6] but there have been a few isolated reports of cardiac involvement. In two patients the cyst encroached upon the pulmonary artery; one had a murmur compatible with pulmonary artery stenosis.[7,11] A third patient had hypoplasia of the left pulmonary artery due to the cyst.[8] No auscultatory findings were noted.

Results of physical examination in our patient suggested mitral stenosis. The lack of atrial enlargement on the electrocardiogram and the high position of the abnormal x-ray shadow argued against this and the echocardiogram excluded this diagnosis. Other left atrial abnormalities were still considered possible. The calcium made an intracardiac tumor or left atrial partition less likely but this finding has been described in each[12] (as it has with a bronchogenic cyst[9,10]). The computed tomography of the chest led to the accurate diagnosis. In retrospect it would have been the initial procedure of choice but the murmur of mitral stenosis suggesting intracardiac pathology led to the hemodynamic and angiographic evaluation.

Precise preoperative definition of the location and cause of the mass was essential to determine the severity of the abnormality and the advisability of surgical treatment and to enable selection of the appropriate surgical approach. The latter was important as it allowed avoidance of a midline sternotomy with possible cardiopulmonary bypass in favor of the safer and cosmetically preferable right-sided thoracotomy. It was elected to proceed with an operation in this asymptomatic patient in order to exclude a neoplastic process and because of the uncertain natural history of this bronchogenic cyst which was already compressing the left atrium and left mainstem bronchus.

Unique in its presentation, this case shows the need to consider extracardiac causes of examination findings usually resulting from intracardiac abnormalities and emphasizes the importance of defining mediastinal abnormalities before surgical intervention.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Targeting Immunologic Infertility

TO THE EDITOR: The exact role of immunologic incompatibility in human infertility is unknown. Yet there is no doubt that antibodies that interfere with sperm function can be demonstrated in either the male or female partner of some couples with otherwise unexplained infertility. It has even been suggested that sperm antibody activity be tested in all couples infertile for more than a year.[1] This may not be practical for several reasons in the usual practice that deals with some infertile patients.

How should the patients be selected? What tests should be done for immunologic infertility? A simple plan is proposed with a case report example. The steps are

- If all other causes of infertility in the couple have been ruled out, immunologic testing should be considered.
- If a semen analysis shows agglutinated clumps of sperm or if the motility is very low, immunologic tests are indicated.
- If results of postcoital tests (Sims', Huhner tests), which are *properly timed* as shown by basal temperature, are consistently abnormal, immunologic testing is definitely warranted.
- The next step should be in vitro testing of sperm-cervical mucus interaction (SCMI). This should be carried out with *controls* of both mucus and antibody free sperm.
- If the SCMI test result is abnormal, the man and woman should both be tested for antibodies to sperm. Controls are also required here.

Report of a Case

A 40-year-old woman, para one, requested reversal of a tubal sterilization carried out five years previously. Her age was not ideal for the procedure, but thorough evaluation was requested by the patient. The investigation gave positive findings of three abnormal postcoital tests (no motile sperm) and less than 10% motility of her husband's sperm. SCMI testing showed *no* penetration of patient or *control* mucus by the husband's sperm, with penetration by control sperm. Antibody tests showed the wife to be negative, but the husband had extraordinarily high titers of agglutinating (1:640) and immobilizing (infinity) antibodies in his serum. The couple could be advised against major surgical treatment.

Discussion

Antisperm antibodies may occur in either the male or female partner. They may be found in serum or in male accessory gland secretions or cervical mucus. Even though the treatment of this condition has been somewhat discouraging the tests are important because there are some options. Condom therapy has been used, as well as low- and high-dose corticosteroid therapy. If the husband is the antibody carrier, sperm washing has been done with insemination or artificial insemination with a donor's sperm can be considered.

In vitro SCMI testing and serum antisperm antibody testing require specialized laboratory capability, but such tests are readily available to practitioners in facilities such as the Reproductive Endocrinology Laboratory at the University of New Mexico Hospital. In fact, the cost is modest compared with that of some standard infertility tests such as hysterosalpingography.

SCMI testing requires control testing and, because properly timed human cervical mucus is not readily available anywhere, bovine mucus is used. Known fertile, antibody free, male donors serve as positive controls.

One action of antisperm antibodies is to agglutinate sperm. The Kibrick test[2] is used for this effect. To detect antibodies that immobilize sperm, the Isojima test[3] is used. Both of these tests to be accurate require both positive and negative controls—that is, serum from donors of known fertility without antibody, as well as known high antibody titer serum.

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Salmonella dublin Infections From Raw Milk

To the Editor: In reading the report in the May 1983 issue by Joshua Fierer, MD, regarding *Salmonella dublin* infections associated with drinking raw milk,[1] I am impressed that nowhere in the article can I find the name of the company that produced the raw milk causing all of these infections. I think it is unfortunate that the author chose not to report the name of the company in the article, as only through public awareness and exposure will there be any likelihood of changing the regulations regarding the certification of raw milk or the institution of social pressures to limit the production of such products.

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Dr Fierer Responds

To the Editor: I quite agree with Dr Schmida that political action will be required if the laws regulating the sale of raw milk in the various states are to be changed. I had hoped that my article would generate concern among physicians who would then be moved to take an interest in this problem. I did not name the dairy that produced the raw milk because, for the reasons I mentioned in the article, it is impossible for any commercial dairy to produce raw milk that is free of *Salmonella dublin*. The problem is inherent in the biology of the infection in cows. Therefore any and all raw cows' milk is a potential hazard, and the number of infections associated with any given dairy will be proportional to the amount of milk they sell.

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Perspective on Risks of Cancer and Genetic Defects

To the Editor: There have been real, quantifiable risks to health associated with exposure to radiation. In most cases, these risks, after exposures to x-rays and radioisotopes during medical diagnosis and treatment or environmentally, have been very small. Nevertheless, physicians and society as a whole have taken many prudent, often relatively simple and inexpensive steps to reduce exposures to radiation. More can clearly be done to further minimize and control this problem.

Unfortunately, there is an hysteria among some members within our society related to radiation. They are attempting to force the enactment of superprecautionary restrictions and safeguards respecting radiation sources, based upon little if any scientific justification.

Cancer and genetic defects concern us all. However, the annual incidence of these attributable to radiation is extremely low—so low that the risks associated with the alternative technologies that would have to be employed in lieu of those involving radiation may be equivalent to or greater than those of the technology being displaced.

We need to place the radiation-associated risks of cancer and genetic defects into a better perspective. The past is not prologue. It is, therefore, not appropriate to project past or current incidence rates 1,000, 10,000 or 100,000 years into the future in order to make the hazard to society seem much larger than it is. Yet, this is what is happening today, even though in those time frames, the earth will probably pass through an ice age, suffer a direct hit by a very large meteor, flip-flop its electromagnetic field, see changes in solar radiation emissions and deposit Los Angeles out into the Pacific and closer to San Francisco.

Technology related to cancer and genetics is moving ahead so fast that at least half of our current medical knowledge and treatments based thereon will be completely obsolete in a generation. Moreover, many of the disease problems that we deal with today will become rare. The advances during the past generation have been enormous and the rate of progress today is even faster. Thus, it is virtually certain that cancer and genetic defects will be much less of a future concern than they are now.

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Gravity Inversion Therapy

To the Editor: Gravity inversion boots are metal and foam rubber devices that clamp around the ankle joint allowing one to hang inverted (−90 degrees) from a horizontal bar. They are being promoted as aids to physical fitness. There have been reports of periorbital petechiae from this practice,[1] but there is a gap in clinical research studies.

After a literature search and personal communication with persons at the National Aeronautics and Space Administration (NASA) and Aerospace Research we found little research has been performed in the (−90 degree) head-down position.[2-4] We found no studies utilizing gravity inversion boots.

In our first study[5] we noted significant elevations in blood pressure, pulse rate, intraocular pressure and central retinal arterial pressure values upon inversion.

In the above study we subjected 20 healthy volunteers from the Chicago College of Osteopathic Medicine student body to a three-minute period of passive inversion, employing gravity inversion boots. The 18 men and 2 women had no medical history of cardiovascular disease or glaucoma.

The subjects were tested seated and inverted for changes in the above-mentioned parameters. Systemic blood pressure was measured at 45 seconds and at three minutes, pulse rates were measured at one minute and central retinal arterial pressure and intraocular pressure were both measured at three minutes.

Systemic blood pressure increased from 119/74

seated (+90 degrees) to 157/93 mm of mercury upon inversion. Central retinal arterial pressure rose from 45/26 to 105/62 mm of mercury, and intraocular pressure from a mean of 19 to 35 mm of mercury. The MacKay-Marg Model 12 applanation tonometer was employed in conjunction with ophthalmodynamometry to measure central retinal arterial pressures.

TABLE 1.—*Comparison of exercise and inversion on central retinal arterial pressure and intraocular pressure. Values shown are mean and standard error for 12 subjects*

	Resting Seated	*Exercise to Target Heart Rate*	*Inverted Position*
Systolic retinal arterial pressure	45± 9.15	78± 9.54*	118± 9.38†
Diastolic retinal arterial pressure	26± 6.06	51± 6.49*	67± 8.08‡
Intraocular pressure	18± 0.55	18± 0.88§	33± 0.99‖

Analysis of variance shows:
*$P<.05$—that is, exercise compared to resting.
†$P<.05$—that is, inverted compared to resting.
‡$P<.05$—that is, inverted compared to resting but not compared to exercise.
§Not significant compared to resting.
‖$P<.001$ compared to resting or exercise.

We wish to report our follow-up work in this area. We chose 12 subjects at random to determine if similar elevations could be induced by rigorous exercise (pulse rate>160 beats per minute).

We found that exercise did not significantly raise intraocular pressure above resting values, and that although central retinal arterial pressure did rise from 45/26 to 78/51 mm of mercury, the increase was significantly less than the rise seen upon inversion (from 45/26 to 118/67 (see Table 1 and Figure 1).

Since the inverted values could not be attained no matter how intense the exercise program in the upright (+90 degree) posture, we speculate that extended periods of head down (−90 degree) inversion could prove to be dangerous in some patient populations, such as those with glaucoma, hypertension, uncompensated congestive heart failure, carotid artery stenosis, hiatal hernia or spinal instability, persons receiving anticoagulants or aspirin therapy, those above age 55 or those with a family history of cerebrovascular accidents.

Since there are now more than a million people using these devices and more than 15 manufacturers of gravity

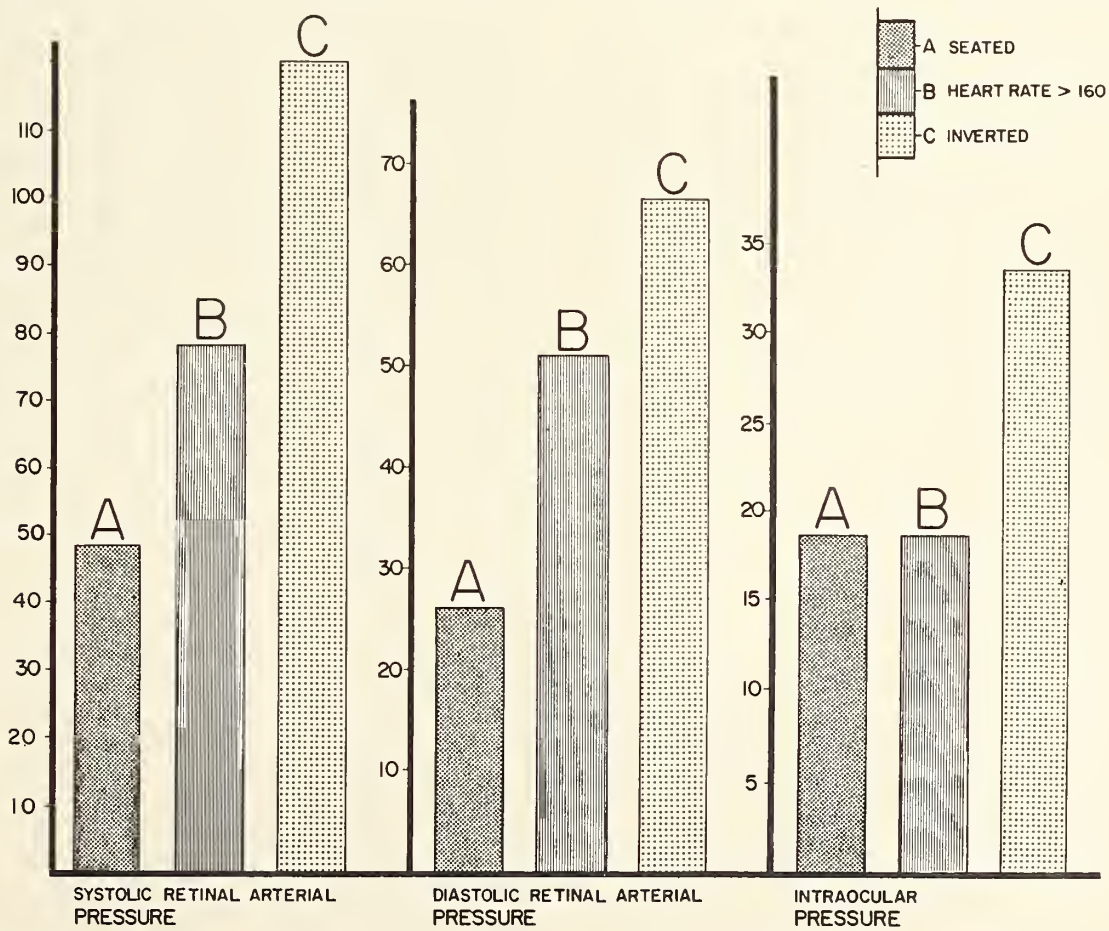

Figure 1.—Comparison of retinal arterial pressure and intraocular pressure: Resting (A), during exercise (B) and during inversion (C). Inversion values were significantly higher than resting values in all cases and significantly higher than exercise values in all cases except diastolic retinal arterial pressure. Intraocular pressure did not rise during exercise.

inversion systems, physicians should be made aware of the potential risks associated with inversion procedures.

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Misleading Blood Pressure Readings

To the Editor: In recent years the control of hypertension has assumed great importance in the therapy and prevention of stroke, heart attacks and renal disease. However, during the past few years it has been called to my attention in several instances that there is an important defect in the technique of taking blood pressure and almost all physicians and nurses are not aware of it.

The first such instance occurred several years ago when one of my patients with hypertension was found to have a normal to low pressure reading when taken by a nurse at the hospital before a minor outpatient surgical procedure. I had just seen him a few days before in my office and he was mildly hypertensive. Then I had several patients who take their own blood pressure readings at home and they reported them as quite normal, but, again, in the office the patients were mildly hypertensive.

This latter state has been attributed by some to office anxiety (*AMA News* Feb 26, 1982, p 26).

Another situation involved patients taking their blood pressure on a machine at a drugstore or supermarket, and invariably those readings were lower than my office readings.

The original event led to the discovery of a common denominator. Being a bit upset over that initial patient's normal-to-low reading, I accompanied him to the hospital and asked the nurse to recheck his pressure in my presence. The patient was seated and the nurse stood at his side; she raised the patient's arm and held it just below her armpit, and proceeded to take his blood pressure and, sure enough, the reading was normal. Then I requested that the nurse repeat the blood pressure test, this time with the patient's arm at his side. In order to avoid bending over and straining her back, the nurse pulled up a chair and took the pressure again and to the surprise of all the reading was identical to my office reading.

The pattern became clear. I recalled when I recently had to go for an insurance physical, the physician had me seated on the edge of the examining table, and held my arm in the crook of his arm while reading the blood pressure; it was the lowest reading I had had in years.

When questioning the patients who took their own home readings, invariably the recordings were taken with their arms on the breakfast table. And the drugstore readings are done with the arm not at the side, but extended forward about 30 to 40 degrees. Whenever I take a blood pressure it is always with the patient's arm at his or her side.

TABLE 1.—*Blood Pressure Readings in 11 Patients*

Patient	*Age, Sex*	*Blood Pressure Medication*	*Arm in Heil Position (mm of Hg)*	*Arm at 90 Degrees (mm of Hg)*	*Arm at Side (mm of Hg)*	*Patient Bent Over (mm of Hg)*
1	68, ♀	0	135/82	138/88	145/90	153/112
2	57, ♀	0	90/55	95/65	105/70	128/87
3	39, ♂	0	100/55	117/60	120/63	132/85
4	62, ♂	0	130/75	148/80	150/85	170/98
5	22, ♀	0	110/70	118/78	128/82	148/105
6	60, ♂	metoprolol tartrate (Lopressor), HCTZ	108/70	118/78	128/83	135/95
7	52, ♀	amiloride HCl-hydrochlorothiazide (Moduretic)	130/85	142/95	148/92	150/105
8	50, ♀	metoprolol tartrate (Lopressor)	108/70	123/78	125/80	138/100
9	50, ♂	metoprolol tartrate (Lopressor), HCTZ	100/60	115/74	128/86	130/100
10	66, ♀	methyldopa (Aldomet), HCTZ	120/60	128/80	140/85	150/100
11	29, ♂	nadolol (Corgard)	105/65	122/78	138/95	140/95

HCTZ = hydrochlorothiazide

In checking through various basic texts used by medical and nursing students, I could find no specific instructions on the placement of the arm during measurement of blood pressure. One patient with a home cuff apparatus did find in the instruction brochure of his machine that the arm should be at the side. It thus appears that the position of the arm is critically important in obtaining an accurate reading on which to base therapy.

Blood pressure readings were taken on a small series of normotensive and hypertensive patients who were receiving therapy. All were seated. Readings were taken with the arms (usually the left) at their sides, so that the cuff and heart were at the same level. Other readings were taken with the arm extended forward at 90 degrees, elevated in the *heil* position and with the patient bent over so the cuff was below the level of the heart by about 2 in. The results are tabulated in Table 1.

One of my patients, an engineer, stated that in a fluid system the static pressure readings taken above the pump or reservoir will be lower and those taken below will be higher.

Concern has recently been expressed over pronounced hypertensive blood pressure readings taken by people using inversion boots. These results may well have been due, however, to the way the readings were taken, with the cuff held below the level of the heart.

When I attended a recent local lecture given by an authority on hypertension from Tulane University Medical School, he told me that he always took blood pressure readings by holding the patient's arm in his armpits, so I thought it was time to publish.

Home readings with arms on breakfast tables and readings on supermarket machines, as well as some professionally taken blood pressure readings, may be lulling some patients into a false sense of security. Further, work should be done with intra-arterial readings with the arms in the above-described four positions to confirm the clinical findings.

If such confirmations hold true, then patients and professionals should all be instructed to take blood pressure readings with the cuff at the same level as the heart, whether the patient is supine, seated or standing.

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Epidemiology of Malignant Disease

To the Editor: I read with great interest Dr Edward Smuckler's article "Chemicals, Cancer and Cancer Biology" in the July issue.[1] Not being specially trained in oncology I found his exposition of the present thinking on the etiology and pathogenesis of cancer most informative.

Publication of this paper is especially timely in view of the indictment by the House of Delegates of the American Medical Association of our news media and politicians for conducting a "witch hunt" against dioxin among a large number of chemicals with toxic potential.

Two matters puzzle me on the epidemiology of malignant disease in general:

1. Although we have in the past half century been living in a period of increasing industrialization with many new chemicals of possible carcinogenicity, statistics quoted in the last part of Dr Smuckler's article show that, with the single exception of lung cancer, the cancer incidence when corrected for age has been stable or in some organs has even decreased.

The likelihood of diagnosing cancer has increased proportionately to the greater availability and better diagnostic facilities today. Is this not indicative of a *fall in cancer incidence* and risk? How can any credence be given to Dr Epstein's prediction, mentioned by Dr Smuckler, of the imminence of an epidemic of neoplastic disease from environmental contamination?

2. In light of the species specificity of nearly all types of cancer why have so much reliance and expenditure of research funds been placed on animal experiments?

In view of the long record of failure to relate the results of these studies to the human experience (saccharin, cyclamates, nitrosamines, formaldehyde, honey and so forth) should not the Delaney clause be amended or even repealed?

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Topics in Primary Care Medicine

Prostatitis: Still a Diagnostic and Therapeutic Dilemma

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

"Prostatitis" is a diagnosis frequently made by primary care physicians and urologists on the basis of symptoms noted by patients and a few clinical findings. However, it is sometimes unclear whether physicians who use this diagnosis are referring to the same entities. If prostatitis is defined as inflammation of the prostate gland as determined by increased numbers of leukocytes in the prostatic fluid, it has been reported that as many as 20% of new patients presenting to a urology clinic have evidence of prostatic inflammation. On the other hand, the variety of other symptoms, signs and findings purported to characterize prostatitis are diverse and poorly understood. Too often prostatitis is diagnosed in any patient who presents with complaints of voiding and ejaculatory disturbances, perineal aching, low back pain and prostatic tenderness to palpation.

To clarify discussion of this problem, prostatitis can be divided into three categories: *acute and chronic bacterial prostatitis, nonbacterial prostatitis* and *prostatodynia*. Those patients with bacterial prostatitis have documented bacterial infections of the prostate. Those with nonbacterial prostatitis have evidence of prostatic inflammation, but no sign of bacterial infection. Those with prostatodynia have complaints associated with prostatitis without bacterial infection or inflammation.

Although few laboratory tests are available to support a diagnosis of prostatitis, two tests are useful in classifying patients who present with symptoms of prostatitis into the correct category. First, patients can be grouped into those who have or do not have bacterial infection of the prostate. True bacterial infections of the prostate are either acute or chronic, and most commonly involve the Gram-negative organisms *Escherichia coli* and *Enterobacter, Serratia, Klebsiella* and *Pseudomonas* species. Collection of segmented urine specimens, as originally described by Meares and Stamey, is the accepted way of diagnosing bacterial prostatitis. To collect these specimens in an uncircumcised patient the foreskin is taped back and the meatus is cleansed with soap and dried; in a circumcised patient no special preparation is needed. When the patient states that he has a very full bladder, he is asked to void and the examiner collects four specimens for quantitative bacterial cultures: (1) the first 5 to 10 ml voided (VB_1 "the voided bladder-1") to show urethral organisms; (2) a midstream specimen (VB_2, "voided bladder-2") to show bladder organisms; (3) prostatic fluid (EPS, "expressed prostatic secretions"), obtained by prostatic massage for culture and microscopic examination, to show prostatic organisms; and (4) the first 5 to 10 ml voided after prostatic massage (VB_3, "voided bladder-3") to show a combination of urethral and prostatic organisms.

Bacterial infection is localized to the prostate if the number of bacterial colonies cultured from the EPS or VB_3 is at least ten times greater than that found in the urethral VB_1 specimen. The bladder urine (VB_2) should be sterile at the time of localization. Isolated examination and culture of prostatic fluid alone (or even cultures of prostatic fluid and bladder urine) cannot be used to diagnose bacterial prostatitis because urethral organisms may contaminate the prostatic fluid specimen during collection and cause misleading results.

The second test, microscopic examination of the

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ABBREVIATIONS USED IN TEXT

VB_1 = voided bladder-1 (the first 5 to 10 ml of voided urine)
VB_2 = voided bladder-2 (a midstream specimen)
EPS = expressed prostatic secretions
VB_3 = voided bladder-3 (the first 5 to 10 ml of urine voided after prostatic massage)

prostatic fluid, will define patients with prostatic inflammation. In patients with nonbacterial prostatitis and acute and chronic bacterial prostatitis, prostatic inflammation usually is shown by the presence of more than 15 leukocytes and occasional oval fat macrophages per high-powered microscopic field (400 to 450 times magnification) of prostatic fluid. Patients with prostatodynia do not have abnormal numbers of leukocytes in their prostatic fluid.

Acute Bacterial Prostatitis

Patients with acute bacterial prostatitis usually complain of a sudden onset of malaise, low back and perineal pain, chills, fever and obstructive and irritative voiding symptoms, such as dysuria, urinary frequency and intermittent urine stream. On prostatic examination there may be a nodular or normal-feeling gland that is painful to palpation. A Gram-negative bacterial pathogen can usually be cultured from the prostatic fluid, but because of prostatic pain and the risk of massage disseminating bacteria from an acutely infected prostate into the systemic circulation, one should probably not perform prostatic massage during the acute illness. Moreover, since bacteriuria is usually present during acute prostatitis, the bacterial pathogen can be cultured from the voided urine specimen, and results of prostatic fluid cultures (EPS) are uninterpretable when the bladder urine is infected.

These patients are often acutely ill and may need to be admitted to hospital for treatment with parenteral antimicrobials, such as aminoglycosides and ampicillin. Once cultures and sensitivities are obtained, treatment with an orally given antimicrobial agent to which the organism is sensitive (such as trimethoprim-sulfamethoxazole, 160 mg/800 mg twice a day) should be continued at full dosage for three to four weeks to prevent the development of chronic bacterial prostatitis. The severe prostatic inflammation in acute bacterial prostatitis allows many antimicrobial agents that would ordinarily be excluded from the prostate gland to enter in concentrations sufficient to cure the infection. In fact, perhaps as a result of this property, acute bacterial prostatitis is probably the most successfully treated of the prostatitis syndromes.

Any bladder outlet obstructive symptoms caused by the inflammation and swelling of the infected prostate are probably best treated with a temporary percutaneous suprapubic drainage catheter. This will prevent further irritation of the prostate that a urethral catheter may cause.

Chronic Bacterial Prostatitis

Patients with chronic bacterial prostatitis present with a variety of symptoms. In some patients intermittent bladder irritative symptoms develop and chronic perineal aching or low back pain occurs, while others are almost asymptomatic even when bacteriuric. Prostatic examination usually reveals a gland which is normal to palpation. The most common characteristic of these patients is a history of recurring urinary infections caused by the same organism. Since the prostate acts as a nidus for these infections, routine antimicrobial therapy clears the bladder infection only temporarily until the prostatic bacteria reinfect the bladder. Patients who present with bacteriuria must be cleared of their bladder infection before lower tract segmented urine cultures can be done to localize the infection to the prostate. This may be done by initiating therapy with antimicrobial agents, such as nitrofurantoin, tetracycline or nalidixic acid, which do not enter the prostatic fluid in significant concentrations. After the patient has taken the drug for several days, segmented urine cultures are collected. To accurately diagnose chronic bacterial prostatitis, these cultures must demonstrate bacterial infection of the prostate, and microscopic examination of the prostatic fluid should show increased numbers of leukocytes and macrophages. Since segmented urine cultures sometimes may be difficult or inconvenient to obtain, especially following transurethral resection of the prostate, long-term antimicrobial therapy may be indicated for suspected bacterial prostatitis if a male patient has had documented recurrent bacteriuria with the same organism and no other source of bacterial persistence can be identified.

The therapy for chronic bacterial prostatitis is often frustrating. Few antimicrobial agents have been shown to diffuse into the prostate and prostatic fluid in concentrations adequate for treatment and cure of the common Gram-negative organisms responsible for infection. Two orally given drugs that may reach therapeutic levels are trimethoprim-sulfamethoxazole (160 mg/800 mg twice a day) and carbenicillin indanyl sodium (764 mg four times a day). When started, administration of these drugs should be continued for at least a month and possibly as long as three months. However, clinical studies have shown that only about 50% of patients with chronic bacterial prostatitis who are treated for 90 days with full-dose trimethoprim-sulfamethoxazole are cured. Although this high therapeutic failure is sometimes due to infected prostatic calculi, it is probably more frequently due to bacterial persistence in prostatic foci that fail to be reached by antimicrobial agents. In those patients in whom treatment fails, daily low-dose antimicrobial therapy with a drug to which the organism is sensitive (such as nitrofurantoin, 50 or 100 mg a day, or trimethoprim-sulfamethoxazole, 40 mg/200 mg a day, half a regular tablet) will prevent relapsing bladder infections and render the patient asymptomatic by sterilizing the urine daily and thereby suppressing bacteriuria.

Although zinc levels from the prostatic fluid of pa-

tients with bacterial prostatitis are lower than those from normal men, there is no convincing evidence that oral zinc administration increases prostatic fluid zinc or that zinc supplementation decreases bacterial or nonbacterial prostatitis. Transurethral resection of the prostate is curative in fewer than 50% of patients with bacterial infection. This is probably because the bacteria tend to be located in areas of the prostate that are not routinely removed in this operation. Thus the side effects of transurethral resection of the prostate, such as retrograde ejaculation, and the suboptimal success rate may render this therapeutic option unacceptable to many patients with bacterial prostatitis; however, these patients are best referred to a urologist for consideration of different modalities of treatment.

Nonbacterial Prostatitis

Patients with nonbacterial prostatitis may present with complaints indistinguishable from those of chronic bacterial prostatitis but without documented episodes of bacterial cystitis. Often they complain of perineal discomfort, and prostatic examination reveals a normal prostate. Although some studies have implicated mycoplasma and chlamydiae as causes of nonbacterial prostatitis, these agents have not yet been proved to be responsible for most cases. Microscopic examination of the prostatic fluid shows inflammation with increased numbers of leukocytes, but segmented urine cultures reveal no prostatic foci of Enterobacteriaceae. It has been reported that in 75% to 80% of men with prostatic inflammation no infectious agent can be found.

Because the source of inflammation in this disease is unknown, therapy is usually unsatisfactory. Because chlamydia and mycoplasma are difficult to culture and are not even sought by most bacteriology laboratories, a therapeutic trial with tetracycline (500 mg four times a day) or doxycycline (100 mg twice a day for two to three weeks) or erythromycin (500 mg four times a day for two to three weeks) is reasonable. However, if no improvement occurs, use of an anti-inflammatory agent like indomethacin or ibuprofen will sometimes give symptomatic relief. Finally, the patient should be counseled that he does have inflammation of his prostate, but it is not related to known infections, cancer or venereal disease.

Prostatodynia

Patients with prostatodynia suffer from a variety of perineal, ejaculatory and voiding complaints that are similar to those observed in patients with chronic bacterial or nonbacterial prostatitis. Examination shows a normal prostate; segmented urine cultures for prostatic localization show no evidence of prostatic bacteria, and these patients, as is true for those with nonbacterial prostatitis, give no documented history of bacteriuria. However, these patients differ from those with nonbacterial prostatitis because microscopic examination of the prostatic fluid shows no evidence of inflammation; hence, this is not a true "prostatitis." The cause of the symptoms in these patients is not understood. Studies have shown that psychologic disturbance, pelvic and perineal muscle spasm, and abnormal spasm of the urethral sphincter during voiding may contribute to a patient's symptoms.

Because there probably are multiple causes for the findings in prostatodynia, no single therapy is effective. Most treatments for the other prostatic syndromes are unsuccessful when applied to patients with prostatodynia because neither inflammation nor infection is present. For those patients who are thought to suffer from abnormal sphincter spasm during voiding, a trial with an α-adrenergic blocking agent such as phenoxybenzamine hydrochloride, 10 mg at bedtime or twice a day, or a muscle relaxant such as diazepam, may produce symptomatic relief. Patients with persistent complaints of frequency, voiding discomfort and suprapubic pain may need to be evaluated for the presence of a bladder tumor, carcinoma in situ or interstitial cystitis. If these abnormalities are absent, the patient should be reassured that no serious disorder has been discovered and that his symptoms are unrelated to venereal disease or cancer. Furthermore, he should be told that his symptoms may intermittently disappear and reappear.

Summary

Although diagnosis of the prostatitis syndromes is often cumbersome and therapy sometimes disappointing, classification of these syndromes allows a more rational therapeutic approach toward treatment of these patients. By carefully selecting patients who have bacterial infection of the prostate, the physician may identify those who may respond to a course of antimicrobial agents. However, because in most of those with nonbacterial prostatitis and prostatodynia there will be no response to antimicrobials, the administration of multiple long courses of such agents can be avoided. Likewise, use of anti-inflammatory agents in patients with prostatodynia can be avoided, and other approaches such as α-blockers or even psychotherapy may be tried.

Though some patients with bacterial prostatitis or nonbacterial prostatitis, and even an occasional patient with prostatodynia, may be cured with present means, the optimal curative treatment remains unknown. Future work defining the causes of nonbacterial prostatitis and prostatodynia may provide new approaches to their management.

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Public Health and Preventive Medicine

Preventable Dental Disease

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One of a series of articles from western state public health departments

A combined effort by medicine, dentistry, public health and consumers has begun to reduce the incidence of dental caries. Physicians now have encouraging news for their pediatric and adult patients. At the same time, the prevalence of periodontal disease is increasing as the population of older adults grows. Physicians share a responsibility with dentists to prevent cavities, periodontal disease and tooth loss. They also have an obligation to keep abreast of changes in dental care delivery as well as the state of the art of prevention.

Fluoridation of water supplies substantially reduces the prevalence of dental caries, especially among children, but is not effective against periodontal disease and subsequent tooth loss. Bohanon and co-workers[1] reported that DMF (decayed, missing and filled teeth) scores for children in areas with fluoridated water were about one-half those in nonfluoridated areas.

However, the reduction in caries during the past 30 years cannot be attributed solely to water fluoridation.[2] The prevalence of dental caries has decreased in communities with nonfluoridated water.[3] From 1972 through 1979 the decline of caries in children living in nonfluoridated communities ranged from 17% in Ohio[4] to 60% in Brockport, New York.[5] The reduction is thought to be largely the result of fluoride ingestion and application through other modes including the unintentional use of fluoridated water in food processing and the increasing use of infant formulas with high fluoride content and of fluoride toothpastes.[5] Also, many dentists apply fluoride topically to the teeth of children.

In addition, educators, school nurses and parents, with professional support from physicians and dentists, are providing school-based dental disease prevention programs. In California,[6] for example, a state-funded program is available for children from kindergarten through sixth grade. Traditional health education and fluoride mouth rinse programs have been augmented with supervised daily deplaquing programs.[7] The curriculum provides instruction regarding the relationship of dental caries to the frequent consumption of cariogenic foods, and emphasis is placed on personal responsibility. We suspect that such programs have contributed to the cumulative effect resulting in the decreased prevalence of dental caries. (This question is now being studied at the School of Dentistry, University of California, San Francisco.) Dental disease is preventable, yet it continues to be the most prevalent disease of school children. This antithesis continues to be a challenge.

Adults have an astounding prevalence of preventable gum disease and subsequent tooth loss. About 45% of the population older than 65 are edentulous and 60% older than 45 who have teeth have periodontal disease.[5] With concerted preventive effort it should be possible to reduce these percentages. Physicians are in a favorable position to counsel patients about the importance of oral hygiene, good nutrition and the benefits of retaining natural teeth as long as possible. Inquiring about food preferences and snacking habits affords opportunities to instruct patients and to encourage them to adopt a noncariogenic diet. Children who learn and practice proper brushing and flossing will have far fewer dental problems throughout life. Adults who have not yet established these habits should understand that the accumulation of food debris, plaque and calculus on and between teeth and at the junction of teeth and gums leads to a chronic inflammatory condition with early loss of teeth.

Profound changes are occurring in methods of dental care delivery. Pressures are growing to lower costs and competition is increasing.[8] More and more young dentists are accepting contracts or concessions in hospitals and health maintenance organizations, as well as department stores, shopping malls and other places formerly

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considered unprofessional.[9] New forms of dental practice may serve more people, including some busy people with one-stop shopping habits, but whether such services will be rendered at reduced cost and will reach many who are not now being treated remain moot questions.

Physicians have a fourfold responsibility for preventing dental disease. Examination of the teeth and gums is only the beginning. A holistic approach requires counseling that will promote lifelong dental health. Patients with dental caries, periodontal disease or severe malocclusion should be referred to a dentist for preventive education and treatment. Most important, physicians can give their support to state and local dental societies and community programs designed to prevent dental disease.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Intravenous Streptokinase After Myocardial Infarction

QUESTION:

Is intravenous streptokinase therapy after myocardial infarction accepted medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Chest Diseases and Internal Medicine, intravenous streptokinase therapy administered promptly after onset of myocardial infarction is not established medical practice. Because of the excessive risks of bleeding associated with this therapy and as yet inadequate comparisons with other therapeutic approaches to the management of acute myocardial infarction, intravenous streptokinase therapy in this setting should continue to be considered investigational.

The short-term and long-term benefits of this therapy are yet to be defined. Currently the National Heart, Lung and Blood Institute is conducting prospective, randomized clinical trials in multiple centers to assess the benefits and problems of both intravenous and intracoronary streptokinase treatment. Although individual reports as well as pooled results from other randomized trials indicate a reduction in immediate mortality after myocardial infarction was treated with intravenous streptokinase, most of those studies antedated the use of other modalities now considered to represent standard practice. Further, the various trials that were pooled retrospectively had not been designed with uniform protocols as a prospective study.

Further investigation is required to document the safety and greater efficacy of this treatment before establishing it as accepted medical practice.

Informed Opinion

A Possible Psychoneuroimmunologic Basis for Recurrent Genital Herpes Simplex

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Genital herpes simplex is a vexing problem for both patients and physicians. For patients afflicted with herpes simplex, the chronic and recurrent nature of the disease, coupled with the therapeutic intractability of the malady, fosters a sense of anguish and helplessness that leads some to despair of ever recovering. For physicians, the therapeutic dilemma of destroying the latent viral genome of herpes simplex within the privileged sanctuary of an infected host's sacral ganglia represents a task that is presently beyond their medical scope. The therapeutic alternatives available to physicians, limited as they are, and the peculiar biologic behavior of the herpesvirus within the protected confines of the neural tissue, sometimes create a defeatist attitude towards both the disease and medical intervention.

The sad dicta "learn to live with it" and "nothing can be done" have frequently been conveyed to patients by physicians experienced with genital herpes simplex. This "hanging of crepe" strategy[1] only serves to increase the pessimism and compound the depression of an afflicted person; this type of "truth telling" of conveying a grim outcome of disease can, like a voodoo doctor's hex, be self-fulfilling.[2] Belief in the certainty of a bad prognosis can create feelings of futility and despair that hinder recovery.

Data from an epidemiologic survey of 375 patients with genital herpes simplex[3] seem to support the apparent futility of therapeutic intervention in the recurrent form of the disease. Yet this apocalyptic judgment with its apparent support for therapeutic nihilism, logical and scientific as it may seem, is faulty and the conclusion is fundamentally flawed, for it fails to take into account the basic immunologic forces within patients. These forces are immediately directed against the virus and actually effect recovery (temporary though it may be) from individual episodes of genital herpes simplex. Likewise, there are moral imperatives, for, while herpes simplex may not at this time be curable in a biologic sense, physicians can nevertheless provide succor and support to patients. The negative hypothesis also fails to consider the "magical" component of a physician's ministrations—that is, the physician's reassuring and consoling nature, or the shamanistic ritual of the office visit. Likewise, the possible therapeutic influence of placebos[4] is underestimated by this faulty conclusion.

Regardless of the value of medical intervention, the fact remains that genital herpes simplex has a profound influence on patients' emotional well-being. It is generally acknowledged that patients' psychologic perception of illness and their ability to cope have a significant impact on both their body chemistry and their capacity to recover from illness.[5] This view of the duality of mind and body, couched in vague and nonquantifiable psychologic terms, has been generally received with skeptical but tolerant acceptance by the medical community. Only recently has a more scientific psychophysiologic basis for this conclusion been elucidated, and the neurochemical mediators that govern these processes defined.[6,7]

Evidence is emerging that emotional stress and anxiety surrounding disease are integrated through hypothalamic centers in the brain, which in turn trigger neurohumoral mediators that may react with receptor lymphoid cells to suppress the immunologic capacity of the host.[8] Before examining in some detail the molecular basis for this proposed psychoneuroimmunologic axis, it seems appropriate to consider some of the psychodynamic conflicts occurring in patients who have recurrent genital herpes simplex. It is also important to examine the media's perception of the dis-

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ease as it affects patients. Finally, it is necessary to understand the dilemma of a physician confronted with a patient with recurrent disease.

Psychologic Factors

For some patients the initial episode of genital herpes simplex is terrifying, given the almost universal, though incorrect, perception that the disease is incurable and that there is nothing to be done. Likewise, a limited understanding of the condition, or spurious information gleaned from friends or the news media, often exacerbate their fears. Aside from the pain, fever and toxemia that often accompany primary genital infection, many patients' first reactions are those of anger and resentment vented against the sexual partner who is thought to be responsible for the infection. In other situations, the reactions include bewilderment and confusion, as patients whose sexual consorts do not have the disease vainly attempt to understand the means whereby they became infected (autoinoculation, asymptomatic viral shedding or reactivation of previously latent disease). Regardless of the circumstances, patients are confronted with a situation that is alien to their prior medical experience: They are infected with a disease that strikes at their most basic biologic drive; there is no apparent way to rid themselves of the virus, and they perceive themselves to be physically and emotionally stigmatized.

Patients who have the recurrent form of genital herpes simplex often feel depressed and vulnerable as a consequence of the infection; they convey feelings of sexual isolation and lowered self-esteem. They often become pessimistic over the repeated failures of various therapies to alter the course of their disease. Genital herpes simplex infection often comes to dominate a major part of their daily thoughts and the impact of the infection on their sex life is often devastating. Relationships with actual or potential sexual consorts become colored by worry over the communicability of the infection. Real or imagined concerns about the disease result in withdrawal of some patients from interpersonal relationships, while others choose celibacy as a permanent and established mode of behavior. Some persons have conveyed the irrational belief that the infection is a penalty for real or imagined transgressions in life.

This recitation of patients' attitudes towards their malady may be viewed by some as melodramatic, if not exaggerated. Yet the psychic toll exacted by genital herpes simplex on sufferers is unique, given the protracted course of the disease and its maddening recurrences. The dimensions of emotional suffering and personal tragedy resulting from genital herpes simplex have not been previously documented. Among the comments made by patients during our own epidemiologic survey, the following quotes are representative:

The continuing outbreaks of herpes simplex make me suicidally depressed. I am hideously unhappy and constantly depressed.

Highly sobering . . . very destructive. The "kiss of death" upon any hopes of sexual fulfillment and its broader implications.

It's a crippling and depressing disease. It makes me angry that I am afflicted, and despite my best efforts it continues to plague me.

It is dreadful and has destroyed my sex life. My husband's, too. It is fortunate that we really had a full sex life previously and therefore are content to be friends. We are completely faithful, but it is really a shame.

Herpes made my life so miserable that I wanted to commit suicide. I don't believe I will ever be healed and normal again.

I am embarrassed at having it and find it difficult to inform a new sexual partner at the beginning of a relationship for fear of what he might think.

The Communications Media

Genital herpes simplex infection has attracted national attention in the lay press, radio and television. The common perception of the public—fostered by members of the communications media—regarding the incurability of the disease and its intractability to conventional medical management have created a profound degree of anguish and despair among those afflicted patients who derive their primary information about the disease from nonmedical sources.

While reporting on the national epidemic of genital herpes simplex, the news media and slick cover magazines have often unnecessarily sensationalized the problem. Lurid headlines have appeared trumpeting the Dantean nature of the affliction: "Herpes Simplex: The New Sexual Leprosy" *(Time,* July 28, 1980, p 76), "A New Incurable Venereal Disease Called Herpes Is Sweeping the Country" *(People,* October 1, 1979, pp 49-54) or "Lovesick: The Terrible Curse of Herpes" (*Rolling Stone,* March 4, 1982, pp 23-24). The articles go on to document some of the known medical facts about genital herpes simplex, but offer readers little hope of recovery, or even respite from the disease. Reporters seem more intent on clever style and journalistic embellishment than on a calm exposition of a sensitive subject. As but one example, stated in the *Time* article, was that ". . . the 'virus of love' infected entire college dormitories and rode the wave of rising divorces and crumbling monogamy." The author went on to say that when patients seek medical help, they will be given ". . . incorrect information and false hopes for cure." As if to infer that a patient is something of a pariah, the article ended with a flip anecdote that after a patient had been informed by his physician that he had herpes, the physician refused to shake hands with him as he left the office.

Genital herpes simplex has also received national attention on many talk shows on both radio and television. Television coverage of the issue by *60 Minutes* (CBS-TV, "400,000 New Cases Each Year," March 4, 1981) dwelt on the personal tragedies of a number of persons infected with the disease. A highly select group of patients belonging to a self-help chapter of the American Social Health Association was interviewed. Little emphasis was placed on the fact that the group consisted exclusively of persons with chronic infection who banded together in an association formed for educational and supportive purposes; thus the group was not representative of the general population of patients.

The *60 Minutes* segment covered the concerns of some members over communicating the infection, their fears of infection during pregnancy and their anxieties about cancer being induced by herpes simplex. Listening to the tragic stories led some viewers with whom I counseled to believe their own clinical courses would be chronic, that they would never be able to have a family and that they were doomed to acquire cervical cancer. Anecdotal reports and testimonial comments thus became the perceived verities by which the public came to understand that herpes simplex was a tragic and hopeless problem. Only a small portion of the television program was devoted to physicians and health professionals whose scientific statements could scarcely undo the negativism and hopelessness conveyed by the program. While the narrator intimated that there were new therapeutic agents on the horizon, no effort was made to highlight the fact that—pregnancy and cervical cancer aside—genital herpes simplex was essentially a trivial temporary infection in which most patients eventually experience long periods without recurrences.

Physicians and Genital Herpes Simplex

Physicians understandably retain a strong belief in the ability of drugs to effect recovery from illness. Whereas they have the intellectual awareness that the apparent response to therapy is sometimes the consequence of the natural course of the disease, they nevertheless commonly attribute their own intervention as the primary means whereby their patients recover. This confidence in the sometimes miraculous properties of modern drugs has a firm foundation in truth. Each year new and increasingly sophisticated pharmaceutic agents are introduced to broaden physicians' armamentaria.

For physicians confronted by patients with chronic recurrent genital herpes simplex, however, the therapeutic cupboard is often bare, given a patient's failure to have responded to previous treatment. Reports in scientific journals are often the primary source wherein physicians first learn of newly available forms of treatment. As new drugs reach the early stages of clinical testing, or as studies appear that suggest that older drugs have shown therapeutic benefit against genital herpes simplex, there is often an enthusiastic rush to administer these agents. Hope rises in both patient and physician alike that the new treatment will bring surcease from the maddening recurrences.

A beguiling list of purported remedies and cures for genital herpes simplex infection has appeared in scientific publications touting the benefits of ether, heterocyclic dyes and light, idoxuridine, vidarabine (adenine arabinoside) and other such topically applied agents. In addition, medical journals have carried articles at various intervals on the initial success of heterologous vaccines such as smallpox, influenza, poliovirus and bacillus Calmette Guérin or homologous vaccines such as Lupidon G (Hermal-Chemie Kurt Herrmann, Hamburg, West Germany) and herpes simplex antigen as hoped-for "magic bullets." Subsequent reports of double-blind trials have shown the many topical and systemic remedies to be without merit as compared with placebos. In some instances the potential hazard of treatment, such as the possible risks of smallpox immunization, may have outweighed any intrinsic placebo benefit.

Because of the apparent failure of modern medicine to find a simple cure for genital herpes simplex, patients' perception of the desperate nature of their affliction has intensified. The view that physicians cannot "cure" their disease has spurred some patients to turn to nonmedical sources for care and information. Disenchanted with the medical profession, some patients have sought help from various organizations and cults promising relief from the relentless problem. A good deal of superstitious dogma and naive assertions, carefully dressed up as authenticated fact, have been laid before the public both from medical and nonmedical sources. Anecdotal reports, testimonial letters and uncontrolled clinical research on agents such as L-lysine, vitamin C, zinc tablets and even yogurt have been accepted by some as scientific fact. Failure to respond to each and every newly suggested treatment reinforces a patient's belief that all treatments are worthless.

The therapeutic pendulum thus swings widely from do-nothing approaches to a try-anything attitude. Sadly, both patient and physician develop a mind-set that nothing works and there is little to be accomplished by traditional medical standards. "Learn to live with it" becomes the implicit message.

The Psychoneuroimmunologic Basis for Herpetic Recurrence

Whereas herpes simplex infection of the lip is no less an infectious disease and affects a far larger number of persons in the United States, the development of recurrent lip lesions does not carry the same impact on a patient's psyche as that of the genital variety of the disease.

Our epidemiologic survey indicated that an unusually large number of patients (86%) claimed that emotional stress activated their genital herpes simplex infection. Aside from its incitant nature, it may be speculated that the chronic emotional stress engendered by this recurrent infection may also impede recovery from infection.[5] One should be careful to note that while emotional stress may trigger attacks, it does not follow that specific behavioral traits lead to or actually cause disease. It is a punitive myth to interpret the development of chronic, recurrent genital herpes simplex, or any disease, in purely psychologic terms.[9] It should also be emphasized that genital herpes simplex is often considered to be activated by factors other than emotional stress. Drug-induced immune suppression, coital friction, overexertion, sleeplessness, menstrual provocation and masturbation have all been implicated and generally do not have psychologic equivalents. But the anxiety and depression that beset many patients with chronic recurrent genital herpes

simplex may have important and pervasive influences on the recurrences.

Evidence linking recurrent genital herpes simplex to biochemical alterations induced by the hypothalamic perception of emotional stress is both complex and tenuous. A full understanding of these influences will not be available until there is a better grasp of the exact neurochemical mechanisms in the sensory ganglia that hold the viral genome of herpes simplex in check.[10] Correlations between aggressive psychopathic states and high titers of antibodies to type 1 herpes simplex virus have been reported,[11] albeit there are contrary views.[12] Likewise a relationship has been established between virus-neutralizing antibodies and mental illness,[13] including psychotic depression.[14,15] Findings of studies have suggested that latent herpes simplex of the brain might inhibit biogenic amines and thus be responsible for psychiatric disease such as depression,[14] though the view of herpes simplex virus as the proximate cause of affective disorders seems farfetched. Nevertheless, low-grade herpes simplex encephalitis has been implicated as the cause of periodic organic psychosis in at least one reported case.[16]

While the intraneuronal mechanisms governing the maintenance of herpetic latency are poorly understood, there are intriguing clues that the mechanisms influencing activation of genital herpes simplex from latency may, in part, be related to adrenergic stimuli. In one study,[17] herpetic keratitis was reactivated in rabbits by administration of epinephrine. Additional support for an adrenergic trigger mechanism was found in a study of rabbits latently infected with herpes simplex virus. Neither cortisone nor pyromin, a drug that raised rabbits' temperature, activated latent disease. Of ten animals given epinephrine, however, six had reactivation of herpes encephalitis.[18] Whereas the release of epinephrine and cortisone are well-known accompaniments of acute physical stress in humans,[19] there is substantial evidence that mental and emotional stress result in profound alterations of the adrenal medullary response, levels of norepinephrine in the brain and a host of other endocrine responses.[20] Study of the interplay between hormonal alterations induced by emotional stress in humans and actual physical impairment in health wrought by these biochemical influences has constituted the life work of Hans Selye.[21]

Close links between emotional stress and herpes simplex infection have been noted for some time,[22-26] though there are some contrary views.[27] Herpetic recurrences can be triggered by suggestion during hypnosis,[28] and psychotherapy has been shown to be effective in terminating recurrent episodes of herpes simplex.[22] Studies of the favorable response of patients who have recurrent herpes simplex to the administration of placebos[29,30] further support the strong links between the disease and a patient's emotions. The precise mechanism whereby placebo administration benefits patients with herpes simplex is not understood, but a lessening of anxiety and a positive expectation of recovery brought about by a physician's intervention may be of major significance.

A recent book[6] has dwelt in great detail on the subject of a "psychoneuroimmunologic axis" as an integrated unit that has significant influence in governing immunity of a person to infection, and even to cancer. It is believed that the hypothalamic perception of stress may set into motion humoral mechanisms influencing pituitary function or other biochemical mediators that have ultimate and profound effects on immune regulation. In support of such a hypothesis, studies in rats have shown that electrolytic lesions in the anterior hypothalamus produced changes in the cellularity of lymphoid tissue and decreased responsiveness of lymphoid cells to concanavalin A.[31] The effect on immune suppression was seen four days after the lesion was produced, but the immune response returned to normal within 14 days. The changes were not mediated through the release of corticosteroids.

The surface membranes of circulating lymphocytes contain hormonal receptors that may respond to neurohumoral mediators.[32] Thus it may be hypothesized that the central nervous system influences immunologic functions by fluctuations in the release of neurohormones that alter the lymphocyte plasma membrane, thereby rendering the immunologically competent cell less responsive in its surveillance role. Chronic stimulation of the hypothalamus induced by continued emotional stress might theoretically result in prolonged immunosuppression through the release of these neurosecretions. In support of such an explanation, Roszman and Brooks showed that patients harboring brain neoplasms, some of which were adjacent to the hypothalamus, were profoundly immunosuppressed, as determined by a variety of in vitro and in vivo immunologic measures.[33] Other anatomic explanations, largely unexplored, have shown the existence of sympathetic pathways between neural centers and immunocompetent tissue.[34]

In addition to the neuroregulatory influences of the hypothalamus on immune function, a number of laboratory investigations have advanced the thesis of stress-induced modulation of the immune system[35] and behaviorally conditioned immunosuppression.[36] Such studies have documented alterations of B-cell and T-cell function as a direct consequence of stress-related events. Extensive research focusing on behaviorial characteristics supports the fact that about 70% of physical illness occurs when patients feel helpless or hopeless.[37] In another study,[38,39] stress-induced immune suppression was observed as alterations of B-cell and T-cell function in 26 bereaved spouses. Furthermore, responses to phytohemagglutinin and concanavalin A were significantly diminished in the bereaved group, though the actual numbers of B and T cells were normal, as were plasma cortisol levels. The findings of measurable alterations in immune function resulting from the stress of bereavement lend credible support for the fundamental concept of stress-induced changes

in the immune response. Adrenocorticosteroid-induced suppression of lymphoid function is another well-known phenomenon[40,41] and may itself lead to a degree of immune suppression.

The links associating the emotional state of patients who have genital herpes simplex infection with regulatory influences on host immunity or reactivation of disease from latency are indeed tenuous, but there is evidence that patients with recurrent herpes simplex do have subtle deficiencies in immunologic responsiveness.[42] There are intriguing, though peripheral, clues that pharmacologic agents such as chlorpromazine hydrochloride[43] and lithium[44] may decrease the frequency and severity of recurrent genital herpes simplex infection through their influence on a patient's emotional conflicts, though the effects of these agents on the virus, much like those of other administered drugs, may be placebo in nature.

A Physician's Role in Patient Management

Given the failure to date of traditional medicine to find a cure for genital herpes simplex, what can a physician do in advising and assisting patients? The unalterable fact remains that in attempting to fathom the complex immunologic mechanisms that lead to recovery from infection, it is truly the patient who is the ultimate healer. In encouraging this recovery, one of the most potent tools available to a physician is the confidence placed in the physician by the patient, as well as the physician's knowledge, solace and support. Physicians have traditionally worn the mantle of "healer," and it is this very perception that often leads to a successful therapeutic outcome. Thus in doctor-patient relationships, physicians should bring all their healing skills to bear with weight equal to that of their scientific abilities. This process requires a willingness by a physician to talk things out and to help a patient confront the practical issue of coping with the problem. A sincere and realistic attitude must be cultivated in the patient that in time the recurrences will diminish and the condition improve. The improvement will be a result of a combination of good medical management on the part of the physician and that of the patient's own native immunologic resources; likewise, intellectual and psychologic insights, stress reduction and an abiding faith in the restorative elements of mind and spirit will effect this result.

Patients should be encouraged to become actively engaged in their own health care, to regain a sense of control over their body, maintain a positive attitude and cultivate an inner sense of peace and reflection. The techniques used in achieving this goal include holistic practices such as meditation, yoga, stress-reduction exercises, conditioned relaxation and even the use of guided imagery in which patients perceive their ganglia as being "cleansed" of the virus. It is important to emphasize that these techniques are not antithetical or antagonistic to traditional medical practices, and patient acceptance of such advice from quite sophisticated persons is remarkably high. For patients with major psychic overlay who are less receptive to this approach, traditional management with psychotropic drugs such as antidepressants should be considered.

Physicians should work towards educating and enlightening their patients as to the natural history of recurrent genital herpes simplex and thus lessening the enormous burden of ignorance borne by some patients. Patients should be instructed to avoid intercourse when they are actively infective, but to follow their regular sexual patterns when they are not. They should be aware that there is some risk, as yet undefined, that they may be asymptomatically shedding the virus.[45] Women should be informed of the importance of frequent Papanicolaou smears because of the association of cervical infection from herpesvirus with cancer, and they should be instructed to seek proper medical advice if they become pregnant.[46] By reducing anxieties about the disease and exposing the many myths about herpes simplex, the negative influences of helplessness and depression can be reduced. A survey by the American Social Health Association of 4,000 members suggested that among the many physician-directed therapies used in management, the single item providing the most lasting benefit was "conscious stress reduction."[47]

Physicians should not emphasize therapeutic nihilism to patients nor convey too gloomy a picture regarding genital herpes simplex infection. There is clear evidence that newly developed antiviral agents such as vidarabine[48] and acyclovir[49] may be effective in the management of herpes simplex in newborns and in immunologically compromised persons, as well as in herpes simplex encephalitis. While not preventing recurrences, these new antiviral agents do represent important advances in patient care. Likewise there is hope that newly developed techniques of injecting neurolytic agents into the skin may spell an end to the maddening local recurrences of infection.[50]

Placebo therapy has been advised in selected cases of herpes simplex,[29,30] but it would be improper to recommend institutionalizing this therapy for all patients. The traditional negative connotation of the word "placebo" should not prevent physicians from recognizing its possible benefits. Whereas some have suggested that the administration of a placebo is deceptive, dishonest and unethical, it is generally acknowledged that physicians who are self-confident, attentive to their patients' emotional needs and who have faith in the treatment they endorse are likely to induce positive health changes merely as a consequence of their behavior.[51] This attitudinal approach to patient care embraced by most physicians can be readily construed to carry the same therapeutic weight as that induced by the administration of a placebo.

Physicians' relationships with their patients and their particular attitude towards illness have a profound influence on the outcome of disease.[52,53] Patients who have genital herpes simplex recurrens do generally im-

prove or achieve long-lasting remissions and, while the time interval to improvement is unknown, it is reasonable to conclude from data gathered in an epidemiologic survey[3] that at least half of the patients have protracted periods of clinical remission within five years of disease onset.

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Information

A Western Version of the Doman-Delacato Treatment of Patterning for Developmental Disabilities

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THE DOMAN-DELACATO treatment of patterning is one of several nonstandard therapies offered children with developmental disabilities.[1] The National Academy for Child Development (NACD) with headquarters in Riverside, California, is billed as a nonprofit parent organization that alleges to bring a new approach to developmental disabilities. The organization is spreading and has chapters in several of the western states. The director is Robert J. Doman, Jr. I will give the historical background of the Doman-Delacato treatment, compare the NACD with the institute that originated such treatment, the Institutes for the Achievement of Human Potential (IAHP) in Philadelphia, and briefly describe, for contrast, components of standard therapy for developmental disabilities, with an emphasis on new advances.

Historical Background of the Doman-Delacato Treatment

Glen Doman, a physical therapist, and Carl Delacato, a doctor of education, originated a treatment for brain-injured children, which is referred to as the Doman-Delacato treatment in the professional literature and patterning in the lay literature. The IAHP in Philadelphia is the main proponent of the theories behind the treatment and its practice. Robert J. Doman, MD, is generally considered the medical spokesman for the Institutes, but other physicians, notably Edward B. LeWinn, MD, and Evan W. Thomas, MD, have also written extensively on the benefits of the Doman-Delacato treatment.[2-4]

Theory

The Doman-Delacato treatment of patterning is based on theories of how ontogeny recapitulates phylogeny, which date back to the 1920s and the 1930s.[3] This recapitulationist theory is not supported by present knowledge of the development of the central nervous system in humans.[5] A concept of "neurological organization," based on these theories, was first proposed by Delacato in 1959.[6] Based on this concept, the IAHP developed the Doman-Delacato Developmental Profile, the main instrument used by the proponents of the treatment to prove its efficacy. This assessment tool has been widely criticized, as summarized and detailed by Chapanis.[7] The importance of establishment of cerebral dominance (lateralization of eye, hand and foot preference to the same side) is prominent in the theory and practice of the Doman-Delacato patterning treatment. Chapanis also reviewed the many studies that have shown that lateral dominance is not important for language and reading functions.

Studies

Inadequacy of theory does not a priori mean that the empirical practice based on such a theory is also inadequate.[5] Testimonials of the cures from treatment from the IAHP have been widely publicized in the lay press. In 1960 Dr Doman and colleagues published in the *Journal of the American Medical Association* a report on the beneficial results of the treatment of 76 children during a two-year period.[8] Neither a control group nor standardized statistical procedures were used and the study results were based solely on the Doman-Delacato Developmental Profile. Using the same profile, LeWinn[2,9] introduced the concept of "angle of change in neurological development" to show "catch up growth," a procedure not suitable for scientific analysis. In 1966 Delacato published ten studies professing to show that patterning treatment improved reading skills in children.[10] Robbins and Glass[11] reviewed these studies and found that they do not stand up to scientific scrutiny. In his own carefully designed studies, Robbins was unable to show improvement in reading using the methods proposed by Delacato.[12,13]

More recently, retarded and brain-damaged children were the subjects in two well-designed studies of the efficacy of the Doman-Delacato treatment.[14,15] These studies used two control groups: one untreated and one receiving the same amount of attention and time from adults as was given the children in the group treated by the Doman-Delacato patterning. The outcome was evaluated on a battery of standard tests using accepted statistical methods of analysis. Neman and co-workers[14] found no dramatic cases of individual improvement and no changes in global intelligence in the treatment group. They showed, however, some minimal positive effects on tests of visual perception and language. Not surprisingly, there was also some improvement on the Doman-Delacato Developmental Profile, which tests program-related responses; that is, the treatment practices for the test. The scientific merits of this study have

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ABBREVIATIONS USED IN TEXT

IAHP=Institutes for the Achievement of Human Potential
NACD=National Academy for Child Development

been debated.[16,17] The second well-designed study showed no effects of treatment.[15]

Critics

The medical "establishment" expressed its concerns about the Doman-Delacato treatment in the late 1960s, even before its lack of efficacy had been shown. An identical statement listing these concerns was approved by most American and Canadian professional and parent organizations for handicapped children and was published in several professional journals in 1968.[18] Some of the concerns expressed were the harmful effects on parents by the promotional methods used, the demanding and inflexible regimen prescribed, the Institutes' assertion that less than 100% effort is useless, restrictions placed on age-appropriate activities of the child, the lack of validity of the Developmental Profile, the undocumented claims for cures and the increased anxiety caused already burdened and confused parents by some of the IAHP criticisms of many typical child-rearing practices. Zigler titled a recent editorial opinion, "A plea to end the use of the patterning treatment for retarded children,"[19] emphasizing the harmful effect the treatment has by raising false hopes and increasing parental guilt. The American Academy of Pediatrics has more recently reviewed the current status of the Doman-Delacato treatment of neurologically handicapped children and issued a policy statement explaining its objections to the treatment methods of the IAHP.[20]

The National Academy for Child Development

The information provided here emanates from promotional pamphlets and newsletters disseminated by the National Academy for Child Development and personal interaction with its director, Robert J. Doman, Jr, on a local live-audience interview television show ("Seattle Today," February 24, 1982), a transcript of which I have compared with my own notes. The NACD does not stress patterning treatment in its literature and neither did Mr Doman on the television program. Instead, it claims to be a charitable, nonprofit parent organization, promoting eclectic treatment of various handicapping conditions for all age groups by providing parent training, using a flexible time commitment and offering no promises for successful outcome.

Nonprofit

The cost of the assessment and training with reevaluation and retraining every three months, as cited by the NACD director on the "Seattle Today" show, was modest. At that time, travel to and from the NACD and room and board while there appeared to be an additional expense. Recent articles in the local press indicate that Mr Doman now holds regular clinics in Seattle, presumably saving families from traveling expenses. However, any expense will be felt by families of handicapped children with their already heavy financial commitments, for example, for transportation and special equipment. The money allegedly supports a director and about ten employees.

Parent Organization

The director stated that the NACD is a volunteer parents' organization run by the parents. Numerous organizations are available to parents of children with specific handicapping conditions, for example, the National Association for Retarded Citizens and The National Society for Autistic Children. It became clear, however, from the comments of the parents belonging to the NACD in the audience at the "Seattle Today" show that they have only one characteristic in common. Regardless of handicap, their children received Doman-Delacato patterning, taught by the NACD staff and provided by the parents in the home. That arrangement makes NACD an unconventional parent organization.

Eclectic Treatment

Mr Doman said that the NACD is eclectic in its treatment, Doman-Delacato being one of the regimens utilized. This claim is difficult to evaluate, as the NACD assessment and treatment programs have not been described in the professional literature. Robert J. Doman, Jr's association with Dr Robert J. Doman at the Institutes for the Achievement of Human Potential in Philadelphia ensures that he is knowledgeable of the patterning treatment. His qualifications to assess the need for and to prescribe other managing modes are not clear from the material available from the NACD. Neither did he specify, during the television program, what other treatments were used. In talking with families who have transferred from the program in IAHP in Philadelphia to NACD in Riverside, California, one detects no change in the *kind* of treatment their children receive, that is, patterning. One suspects that in Mr Doman's mind, the Doman-Delacato treatment is the only intervention that really works and that it works for all children, regardless of their developmental disability.

All Age Groups

Mr Doman made the remark on the television program in Seattle that the National Academy for Child Development works not just with all handicaps, but also with all age groups and currently serves patients from 3 days to 65 years of age. In view of this information, the name chosen for the organization seems misleading.

Parent Training

The promotional literature from the NACD emphasizes that parents are the primary advocates for their handicapped child. Professionals in schools, clinics, hospitals and institutions serving the disabled would

agree. However, NACD also puts great stress on the parents' role as their child's therapist and teacher. One mother on the television program said she spent 56 hours a week on her daughter's therapy. Nobody doubts that a child benefits from that much individual attention. Many professionals are concerned, however, that the therapist role changes the nature of the parent-child relationship. This role also places the burden of treatment failure on the parent.[21] Most professionals encourage parents to learn anything and everything about their child's therapy and educational program, but discourage them from becoming their child's primary therapist and teacher.

Flexible Time Commitment

One of the criticisms leveled by the medical establishment on the Doman-Delacato patterning treatment as prescribed at the IAHP in Philadelphia has been of the demanding, rigid and inflexible time schedule[18,21] (12 hours a day, seven days a week). Mr Doman said on the television program that the NACD encourages parents to spend "whatever time the family has available" on treatment. He also said, "If we can put more in, we should get more out." One family expressed relief to be able to allow only eight hours a day for the treatment of their son (after transferring from the Philadelphia to the Riverside program). Still, this time commitment to patterning would appear not to allow school attendance, adequate peer interaction and a normal amount of recreational activities. Under such circumstances, a disabled child has few opportunities to learn how he or she realistically fits into a world populated with mostly nonhandicapped persons, an important task for a youngster growing up with a developmental disability.

No Promises for Successful Outcome

Another criticism of the Doman-Delacato patterning treatment is that it offers false hope. On "Seattle Today" Mr Doman emphasized that NACD offers no promises for a successful outcome. This point is difficult to evaluate, not knowing what goes on in the interaction between parents and trainers at the NACD. Parents have described the unusual life-style resulting from the patterning treatment in testimonials in the lay literature: space (usually a basement) set aside exclusively for the needs of the handicapped child; a multitude of adult volunteers, mostly strangers, visiting the house every day and working with the child, who is put through prescribed paces of tedious motor movements, breathing exercises, spinning and so forth. One must conclude that only hope keeps parents going—hope that the predictions of previous evaluators were in error and that their disabled child somehow, some day, will be like any other child. In most instances, these are false hopes.

In conclusion, the parent-training program provided by the National Academy for Child Development in Riverside, California, appears to be a slight modification of the Doman-Delacato patterning treatment offered at the Institutes for the Achievement of Human Potential in Philadelphia for years. It is a western version of an old remedy to cure all kinds of handicapping conditions, which has been denounced by parent organizations and professionals working with disabled children and which, in scientifically acceptable studies, has been shown to be essentially useless.

Standard Management of Developmental Disabilities

Proponents for the Doman-Delacato patterning treatment maintain that their treatment somehow reorganizes a proposed neurologic disorganization of the brain and charge that all other treatments are "symptomatic."[4] Standard management indeed aims for symptomatic relief of developmental disabilities and does not claim to be curative. Such management is based on the premises that all children can learn, no matter how handicapped, and that the education of all children is a collective responsibility of our society. Management of children with developmental disabilities might include some or all of the following components.

Medical Management

A primary care physician has an important role as a coordinator of the complex health care needs of children with developmental disabilities, who have an excess of almost every kind of medical problem plaguing normal children and some seen only in handicapped children. Physicians taking care of children are bombarded with claims of benefit from nonstandard treatment of developmental disabilities—for example, dimethylsulfoxide (DMSO), special diets and megavitamins.[1] Aside from the occasional use of medication to modify behavior, drug or special diet therapies are seldom appropriate for handicapped children. Thyroid supplementation in hypothyroidism and a low-phenylalanine diet in phenylketonuria are rare exceptions.

Developmental Assessments

Repeated developmental assessments might be made by a developmental pediatrician, a psychologist or other trained professional, but are ideally done by a developmental team. The purpose for such assessments is twofold: they identify goals for intervention and help parents formulate realistic expectations.

Education

Early childhood development centers are available in most metropolitan areas in the West for children identified to be developmentally delayed. Public school programs take over at various ages, as early as age 3 years in most areas in the state of Washington. PL94-142, the *Education for All Handicapped Children Act* (passed by Congress in November 1975), now mandates educational services for handicapped children. Educational goals are formulated for each child, the so-called Individual Education Plan (IEP). The parents have to agree with the goals and sign the plan.

Thus, educators are accountable to the parents of children with developmental disabilities.

Physical and Occupational Therapy

Developmental centers and public school programs for children with developmental disabilities typically have physical and occupational therapists available to them. The therapists provide both consultation to teachers and individual therapy to children with cerebral palsy. Most therapists working with children in the Northwest are pediatric therapists—that is, trained in neurodevelopmental treatment, also known as the Bobath method. This treatment is based on well-documented observations of the neurologic development of infants and children. Henderson[22] has recently reviewed research on this and other therapy modalities used in children with developmental disabilities.

Speech Therapy

Speech therapists are now often called "communication disorder specialists" to indicate that they also have knowledge of language and communication. New developments in this field include total communication programs for children with severe language delay (sign language used simultaneously with spoken language in classrooms) and technically complex communications boards, which can be used by children with physical limitations of speech.

Parent Support

Support for parents of handicapped children is available in a variety of forms in most communities: from chapters of national parent organizations to individual counseling in mental health centers or by private practitioners. Behavior modification techniques have been used successfully for years by educators and therapists working with handicapped children. Even though written with normal children in mind, Patterson's books explaining the theory[23] and practice[24] of behavior modification are used extensively and successfully by psychologists, social workers and nurses helping parents to live with children with developmental disabilities. Parent-to-parent programs are the newest wrinkle in the parent support system. New parents of handicapped children are put in contact with specially trained experienced parents of children with similar handicaps.

Conclusion

As in many areas of medicine, it is difficult to prove the effectiveness of standard therapies in developmental disabilities. Infant stimulation programs for developmental delays[25] and neurodevelopmental therapy for cerebral palsy[26] have been scrutinized and questioned. In standard treatments, scrutiny and questioning are encouraged.[22] Promising new ideas and techniques are tried and evaluated. They are discarded if found wanting and, if proved beneficial, integrated into already accepted practices. One can only wish that parents would trust this process rather than seek nonstandard treatments. Such treatments, as exemplified by the Doman-Delacato patterning, rely on testimonials and emotional appeal, rather than scientific data, to support their claims of efficacy.

A positive attitude towards children with developmental disabilities and their families by physicians will help keep their patients in the established system. A recent critic of the medical establishment from within the establishment has pointed out that patients often turn to "quacks and healers" when they need care rather than cure.[27] There are few cures for developmental disabilities. It behooves physicians to keep informed of what is considered standard and what is nonstandard treatment for such disabilities, and to reflect to parents and handicapped children that they really do care.

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In Memoriam

California Medical Association

ADAMS, LINUS E., Escondido. Died February 16, 1983, in Escondido, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr Adams was a retired member of the San Diego County Medical Society.

BECKER, GEORGE HENRY, San Francisco. Died July 13, 1983, aged 89. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1921. Licensed in California in 1921. Dr Becker was a retired member of the San Francisco Medical Society.

BOUCH, JOEL ROBERT. Petaluma. Died June 7, 1983, in Petaluma, aged 40. Graduate of Hahnemann Medical College and Hospital, Philadelphia, 1969. Licensed in California in 1971. Dr Bouch was a member of the Sonoma County Medical Association.

BRANNICK, THOMAS L., Napa. Died July 12, 1983, in Napa of cancer, aged 61. Graduate of the University of Illinois College of Medicine, Chicago, 1952. Licensed in California in 1972. Dr Brannick was an associate member of the Napa County Medical Society.

BROWN, GEORGE D., Pomona. Died March 30, 1983, in Pomona, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr Brown was a member of the Los Angeles County Medical Association.

BRUCKMAN, FRED S., San Francisco. Died June 8, 1983, in San Francisco, aged 85. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1931. Dr Bruckman was a retired member of the San Francisco Medical Society.

BULLOCK, LEWIS T., Los Angeles. Died April 7, 1983, in Los Angeles, aged 76. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1930. Licensed in California in 1933. Dr Bullock was a member of the Los Angeles County Medical Association.

DOROSIN, E. DAVID, Palo Alto. Died July 17, 1983, in Stanford of myocardial infarction, aged 51. Graduate of the State University of Iowa College of Medicine, Iowa City, 1956. Licensed in California in 1957. Dr Dorosin was an associate member of the Santa Clara County Medical Society.

FITZGERALD, EDWARD M., San Bernardino. Died July 1, 1983, in San Bernardino of cancer, aged 78. Graduate of the University of Minnesota Medical School, Minneapolis, 1932. Licensed in California in 1948. Dr Fitzgerald was a member of the San Bernardino County Medical Society.

FOLEY, JACK C., Oroville. Died July 27, 1983, in Oroville of cancer, aged 61. Graduate of the University of Buffalo School of Medicine, 1946. Licensed in California in 1948. Dr Foley was a member of the Butte-Glenn Medical Society.

FRY, ORVIN P., Grass Valley. Died March 24, 1983, in Grass Valley, aged 78. Graduate of Rush Medical College, Chicago, 1934. Licensed in California in 1934. Dr Fry was a retired member of the Placer-Nevada County Medical Society.

HAMMON, FRANK P., Visalia. Died July 10, 1983, in Visalia, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1947. Licensed in California in 1955. Dr Hammon was a member of the Tulare County Medical Society.

HUSHAW, JOHN R., Palm Desert. Died February 5, 1983 of injuries received in a lightplane crash near Desert Hot Springs, aged 45. Graduate of George Washington University School of Medicine, Washington, DC, 1964. Licensed in California in 1965. Dr Hushaw was a member of the Riverside County Medical Association.

LINSLEY, C. HARRY, Los Angeles. Died April 1, 1983, in Los Angeles, aged 82. Graduate of the University of Nebraska College of Medicine, Omaha, 1928. Licensed in California in 1930. Dr Linsley was a member of the Los Angeles County Medical Association.

MACOMBER, H. WADE, Burlingame. Died March 1, 1983, in a traffic accident in Redwood City, aged 88. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr Macomber was a retired member of the San Mateo County Medical Society.

MCCULLOCH, CHARLES S., Chico. Died February 17, 1983, in Chico of myocardial infarct, aged 64. Graduate of the University of Nebraska College of Medicine, Omaha, 1943. Licensed in California in 1948. Dr McCulloch was a retired member of the Butte-Glenn Medical Society.

MCMULLEN, JOHN F., Riverside. Died February 3, 1983, in Riverside, aged 73. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1934. Licensed in California in 1947. Dr McMullen was a retired member of the Riverside County Medical Association.

PATERNOSTER, ALFRED A., San Gabriel. Died February 5, 1983, in Arcadia, aged 55. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1956. Licensed in California in 1957. MD degree from California College of Medicine, 1962. Dr Paternoster was a member of the Los Angeles County Medical Association.

ROGER, JOSEPH H. D., San Francisco. Died April 14, 1983, in San Francisco, aged 90. Graduate of Hahnemann Medical School of the Pacific, San Francisco, 1915. Licensed in California in 1915. Dr Roger was a retired member of the San Francisco Medical Society.

SCHINDLER, MEYER, San Francisco. Died April 5, 1983, in San Francisco of myocardial infarct, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr Schindler was a member of the San Francisco Medical Society.

SHANKS, HAROLD J., Pleasanton. Died March 28, 1983, aged 83. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1934. Licensed in California in 1935. Dr Shanks was a retired member of the Alameda-Contra Costa Medical Association.

SIMPSON, BEVERLY, San Francisco. Died May 24, 1983, in Walnut Creek of arteriosclerosis, aged 86. Graduate of Harvard Medical School, Boston, 1924. Licensed in California in 1927. Dr Simpson was a retired member of the San Francisco Medical Society.

SMITH, GREGORY, San Francisco. Died July 9, 1983, aged 73. Graduate of Tulane University School of Medicine, New Orleans, 1934. Licensed in California in 1934. Dr Smith was a member of the San Francisco Medical Society.

STEPHENS, H. BRODIE, San Francisco. Died April 18, 1983, in Santa Barbara, aged 81. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1926. Licensed in California in 1928. Dr Stephens was a retired member of the San Francisco Medical Society.

STERN, RALPH E., Santa Rosa. Died April 2, 1983, in Santa Rosa, aged 35. Graduate of the University of Illinois College of Medicine, Chicago, 1972. Licensed in California in 1975. Dr Stern was a member of the Sonoma County Medical Association.

WEBB, HELEN L., Palo Alto. Died May 6, 1983, in Palo Alto of cancer, aged 67. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1950. Licensed in California in 1958. Dr Webb was a retired member of the Santa Clara County Medical Society.

WHITE, FRANCES ELOUISE, San Diego. Died June 10, 1983, in Mission Hills, aged 59. Graduate of the University of Colorado School of Medicine, Denver, 1947. Licensed in California in 1948. Dr White was a member of the San Diego County Medical Society.

WRIGHT, CYRIL B., Northridge. Died March 30, 1983, aged 79. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr Wright was a member of the Los Angeles County Medical Association.

YOUNG, CORBIN ALFRED, Winters. Died March 10, 1983, of injuries received in a lightplane crash near Rancho Murietta, aged 66. Graduate of Tulane University School of Medicine, New Orleans, 1952. Licensed in California in 1954. Dr Young was a member of the Yolo County Medical Society.

Idaho Medical Association

CLIFFORD, JAMES E., Boise. Died June 3, 1983, in Boise, aged 68. Graduate of the University of Wisconsin Medical School, Madison, 1941. Licensed in Idaho in 1948. Dr Clifford was a past member of the Ada County Medical Society.

HANCHER, HYDEN WILLIAM, Weiser. Died March 30, 1983, in Weiser, aged 81. Graduate of Northwestern University Medical School, Chicago, 1927. Licensed in Idaho in 1929. Dr Hancher was a retired member of the Southwestern Idaho District Medical Society.

HERRON, EMMETT EARL, Grace. Died January 5, 1983, in Grace, aged 63. Graduate of the University of Utah College of Medicine, Salt Lake City, 1946. Licensed in Idaho in 1949. Dr Herron was a member of the Bear River Valley Medical Society.

JEPPESEN, FRANKLIN B., Boise. Died July 13, 1983, in Boise, aged 77. Graduate of the University of Iowa College of Medicine, Iowa City, 1929. Licensed in Idaho in 1934. Dr Jeppesen was a retired member of the Ada County Medical Society.

JONES, CURTIS A., Boise. Died January 4, 1983, in Boise, aged 67. Graduate of the University of Michigan Medical School, Ann Arbor, 1943. Licensed in Idaho in 1943. Dr Jones was a retired member of the Ada County Medical Society.

MOSER, MARGERY M., Cascade. Died January 3, 1983, in Cascade, aged 69. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1951. Licensed in Idaho in 1954. Dr Moser was a past member of the Southwestern Idaho District Medical Society.

MUNN, ELIZABETH L., Caldwell. Died April 9, 1983, aged 72. Graduate of the University of Oregon Medical School, Portland, 1936. Licensed in Idaho in 1937. Dr Munn was a retired member of the Southwestern District Medical Society.

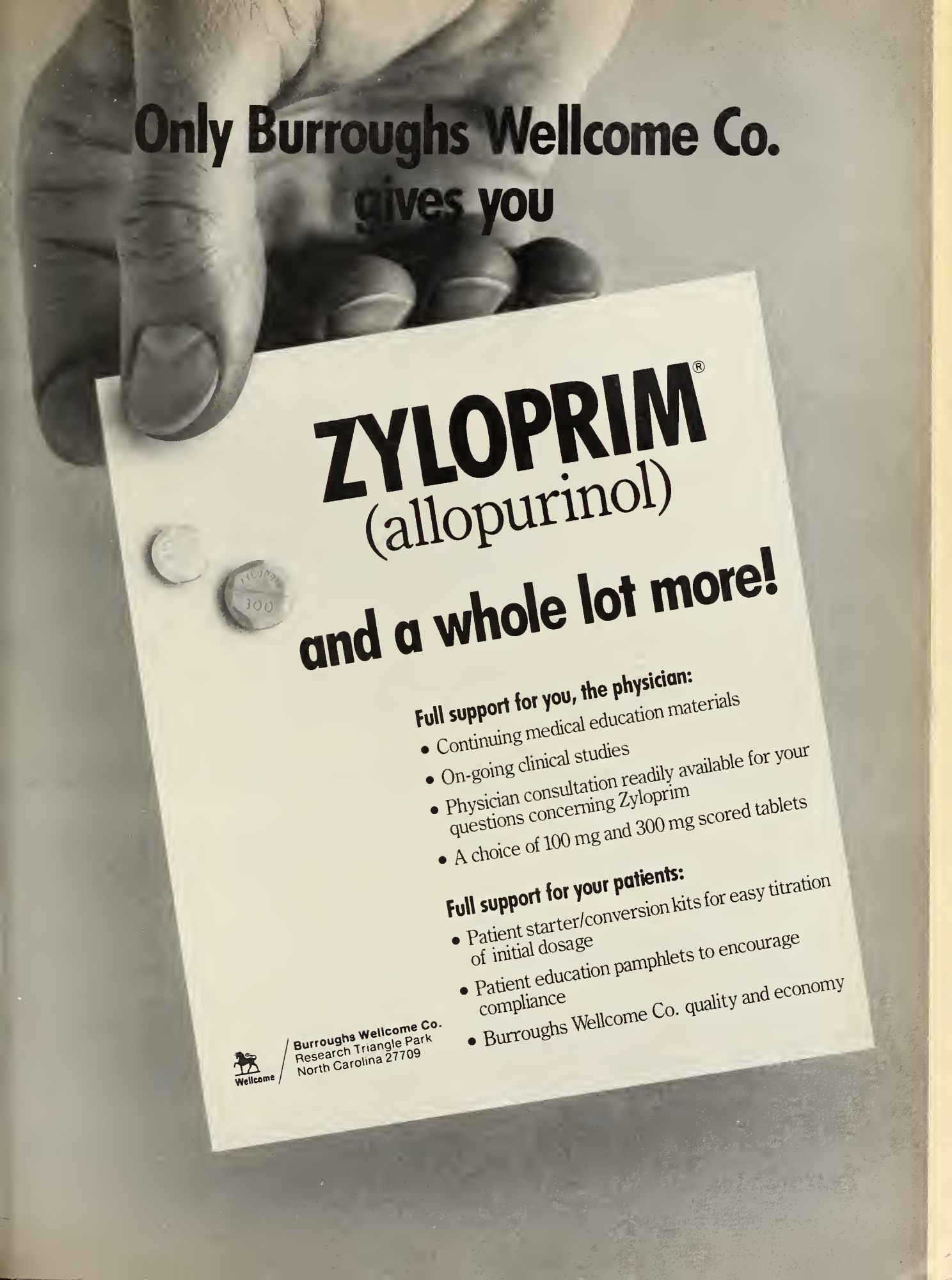
SCYPHERS, JERRY E., Lewiston. Died July 11, 1983, in Lewiston, aged 52. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, Missouri, 1963. Licensed in Idaho in 1970. Dr Scyphers was a member of the North Idaho District Medical Society.

Washington State Medical Association

BLACKSTONE, WILLIAM B., Longview. Died June 14, 1983, in Longview, aged 59. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1949. Licensed in Washington in 1950. Dr Blackstone was a member of the Cowlitz-Wahkaikum County Medical Society.

FRECH, ROBERT S., Bremerton. Died December 12, 1982, in Bremerton, aged 51. Graduate of Harvard Medical School, Boston, 1960. Licensed in Washington in 1971. Dr Frech was a member of the Kitsap County Medical Society.

GERAGHTY, THOMAS P., Sequim. Died June 18, 1983, in Seattle, aged 72. Graduate of the University of Oregon Medical School, Portland, 1939. Licensed in Washington in 1941. Dr Geraghty was a retired member of the Clallam County Medical Society.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Books

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3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

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OBESITY—VOLUME 4 IN CONTEMPORARY ISSUES IN CLINICAL NUTRITION SERIES—M. R. C. Greenwood, PhD, Professor of Biology, Vassar College, Poughkeepsie, NY, and Director, Adipose Tissue CORE Laboratory, Obesity Research Center, Columbia University, New York. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 205 pages, $27.00.

PEDIATRICS—Edited by Harold M. Maurer, MD, Professor and Chairman, Department of Pediatrics, Children's Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 1,038 pages, $32.50.

THE PHYSICIAN'S BOOK OF LISTS—David M. Margulies, MD, Columbia Presbyterian Medical Center, New York, and Malcolm S. Thaler, MD, New England Deaconess Hospital, Boston. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 290 pages, $9.95 (softbound).

PHYSIOLOGY OF THE JOINTS, Volume 1: UPPER LIMB—Fifth Edition—I. A. Kapandji, Ancien Chef de Clinique Chirurgicale, Assistant des Hôpitaux de Paris; translated by L. H. Honore, BSc, MB, ChB, FRCP (C). Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 283 pages, $17.00 (softbound).

RESUSCITATION—Edited by Sheldon Jacobson, MD, Associate Professor of Medicine and Surgery, University of Pennsylvania School of Medicine, and Medical Director, Department of Emergency Services, Hospital of the University of Pennsylvania, Philadelphia. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 133 pages, $20.00.

SCIENCE DEIFIED & SCIENCE DEFIED—THE HISTORICAL SIGNIFICANCE OF SCIENCE IN WESTERN CULTURE FROM THE BRONZE AGE TO THE BEGINNINGS OF THE MODERN ERA, CA. 3500 B.C. TO CA. A.D. 1640—Richard Olson. University of California Press, 2223 Fulton St., Berkeley, CA 94720, 1983. 312 pages, $9.95 (softbound).

THE SOCIAL ORGANIZATION OF DOCTOR-PATIENT COMMUNICATION—Sue Fisher and Alexandra Dundas Todd. Center for Applied Linguistics, 3520 Prospect St. NW, Washington, DC 20007, 1983. 269 pages, $14.95 (softbound). $32.95 (hardbound).

WATSON-JONES FRACTURES AND JOINT INJURIES—2 Volumes—6th Edition—Edited by J. N. Wilson, ChM, FRCS, Consultant, Orthopaedic Surgeon, Royal National Orthopaedic Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 1,280 pages, $175.00.

KNEE PAIN AND DISABILITY—2nd Edition—Rene Cailliet, MD, Professor and Chairman, Department of Rehabilitative Medicine, University of Southern California School of Medicine, Los Angeles. F. A. Davis Company, 1915 Arch St., Philadelphia, PA 19103, 1983. 177 pages, $11.95.

THE LAST DANCE: ENCOUNTERING DEATH AND DYING—Lynne Ann DeSpelder and Albert Lee Strickland. Mayfield Publishing Company, 285 Hamilton Avenue, Palo Alto, CA 94301, 1983. 473 pages, $16.95.

LEGG-CALVÉ-PERTHES' DISEASE—Anthony Catterall, MChir, FRCS, Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital and Charing Cross Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 111 pages, $40.00.

METABOLIC CARE—D. E. F. Tweedle, MB, ChB, FRCS (Ed), ChM, Senior Lecturer in Surgery, University of Manchester, and Honorary Consultant Surgeon, University Hospital of South Manchester, England; with contributions by F. Cockburn, MB, ChB, DCH, RFPS, FRCP (Ed), FRCP (Glas), MD, Samson Gemmell Professor of Child Health, University of Glasgow, and J. C. Stoddart, MB, BS, FFA, RCS, MD, Consultant Anaesthetist and Consultant-in-Charge of the Intensive Therapy Unit, Royal Victoria Infirmary, Newcastle upon Tyne. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 238 pages, $24.50 (softbound).

THE MINDS OF THE CHINESE PEOPLE—Martha Livingston, MA, and Paul Lowinger, MD. Prentice Hall Publishers, Englewood Cliffs, NJ 07632, 1983. 237 pages, $16.95.

MORAL PROBLEMS IN MEDICINE—Second Edition—Edited by Samuel Gorovitz, Department of Philosophy, University of Maryland, College Park, Md; Ruth Macklin, Department of Community Health, Albert Einstein College of Medicine, New York; Andrew L. Jameton, Institute for Health Policy Studies, University of California, San Francisco; John M. O'Connor, American Philosophical Association and Department of Philosophy, University of Delaware, Newark, and Susan Sherwin, Department of Philosophy, Dalhousie University. Prentice-Hall, Inc., Englewood Cliffs, NJ 07632, 1983. 649 pages, $24.95.

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Interested physicians should send CV and reply to: Vern Howe, Pacific Physician Services, P.O. Box 1346, Loma Linda, CA 92354; (714) 825-4401.

WASHINGTON & IDAHO: Modern Free Standing Emergency Centers need physicians. Experience in Family Practice or Emergency Medicine desired. Benefits include flexible work schedules, paid malpractice, competitive compensation, profit sharing and more. Respond with CV to Richland Minor Emergency Center, 310 Torbett, Richland, WA 99352.

PHYSICIANS for new urgent care clinic. Open 80 hours per week. Pay by the hour or salary. Suburb of Tacoma, Washington. Mild climate, boating, skiing. Contact Wayne Larson, MD, (206) 588-5258.

PHYSICIANS WANTED

ORTHOPEDIST for daily 8-5 office practice. Salary negotiable. Send CV to: P.O. Box 162927, Sacramento, CA 95816.

ALASKA: FAMILY PRACTITIONER, Board eligible/certified, to join the Fairbanks office of Alaska's largest multi-specialty clinic. Generous guaranteed salary, benefits, and relocation allowance. Partnership opportunity. Contact: Administrator, Fairbanks Clinic, 1867 Airport Way, Fairbanks, AK 99701.

EMERGENCY PHYSICIAN—OLYMPIA, WASHINGTON. Immediate opening for residency trained or board eligible Emergency Physician to join full-time group serving modern private hospital in southern Puget Sound. Contact Mark Urmanski, MD, P.O. Box 2786, Olympia, WA 98506.

CENTRAL CALIFORNIA. Residency trained physicians for group Family Practice (OB and inpatient). Attractive remuneration, pleasant community, Sierra recreation, teaching opportunities. FAFM, 1921 N. Gateway Blvd., Fresno, CA 93727.

PHYSICIANS WANTED

INTERNIST—Specialist in Internal Medicine desired for progressive mountain community in Northeastern California. Expanding population of recreational and retired is creating an immediate and viable practice opportuity. Clinician is sought with academic and practice credentials to complement dynamic medical staff of primary care physicians and certified Thoracic Surgeon. Located in active year-round recreation area, an excellent quality of life and well-equipped staffed hospital offer a personally rewarding clinical experience. Please contact Administrator, E. Keith Berry, at P.O. Box 737, Chester, CA 96020 for further details and community profile.

PACIFIC NORTHWEST—Family Practice Physician needed for Indian Community Clinic in Washington State. Excellent location, urban setting only minutes from beaches, mountains, cultural activities and CME opportunities. 5 local hospitals. Routine obstetrics. Wash. State License required. Send CV to Puyallup Tribal Health Authority, 2209 E. 32nd St., Tacoma, WA 98404.

CHIEF OF MEDICAL STAFF. California State University, Chico is seeking candidates for the principal medical officer responsible for clinical programs at the Student Health Center. Duties: 25% medical administration 75% direct patient care. Chico is a rural community of 60,000 in the northern portion of the Sacramento Valley with mountains, creeks, friendly people and abundant recreational opportunities. Ten month position with salary to $51,430. Application deadline November 11, 1983. AA/EOE. Submit letter of application and résumé or request for information to Tom Beckman, CSU, Chico, Chico, CA 95929.

FAMILY PRACTITIONER: Tulare County—Board certified Family Practice Physicians to practice in an outpatient clinic system with 13 physicians. Consider a rural lifestyle in central California. Cultural amenities of metropolitan areas easily accessed and the Sierra Nevada mountains nearby. Salary: $75,779 to $79,639 annually. Send CV to Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266 Affirmative Action Employer.

OB/GYN—TULARE, CALIFORNIA—Board certified eligible OB/GYN to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $82,867-$87,090 annually. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. Affirmative Action Employer.

(Continued on Page 564)

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(Continued from Page 562)

POSITION OPEN: Medical Ophthalmologist wanted in large midwest practice that is affiliated with university training program. Excellent medical skills required. Knowledge of Argon Laser preferable. Opportunity to assist in surgery and learn Yag Laser available. Salary $75,000 plus generous benefits and rapid advancement depending on qualifications. Send résumé to: Box 6379, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

SOUTHERN OREGON, Gateway to the Oregon Caves. Needed—rural family practitioner. Medically underserved, high retirement area. Excellent referral system. Lease ½ of existing medical facility, fully equipped. Call AC (503) 592-3916 or 592-2224 evenings or weekends.

ASSISTANT MEDICAL DIRECTOR of a comprehensive occupational medical program in Arizona. The position provides management of occupational injury and disease, evaluation of disability, job placement, periodic executive health evaluations, health education, employee counseling, clinical supervision of nurses and counselors and some direct clinical activities. An Affirmative Action/Equal Opportunity Employer. Submit résumé to Box 6390, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

PED/RAD/INTERNIST - GP/ORTHO/SURG/OB/GYN/FP for established growing, multi-specialty practice in sunny Los Angeles. Guaranteed salary and benefits first year, then incentive based on productivity. Spanish very helpful. Ownership potential, growth capability. Respond with CV: Med. Dir., Box 6377, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

CALIFORNIA—Family Practice Department of 60-man multispecialty clinic seeking physician for acute care/occupational medicine. BC/BE. Salary leading to partnership. Central valley near Sacramento. Contact R. H. Holland, MD, Woodland Clinic, Woodland, CA 95695. (916) 666-2466.

CALIFORNIA FAMILY PRACTICE. Two FP residency trained physicians needed for new primary care clinic in Fremont, Calif to open in the spring or summer of 1984. Clinic affiliated with Palo Alto Medical Clinic. No OB. Salary, vacation, meeting time, malpractice. Send CV to William E. Straw, MD, 300 Homer, Palo Alto, CA 94301.

WANTED. Group of one psychiatrist, two clinical psychologists, and a psychiatric social worker are seeking a Board certified or Board eligible general psychiatrist to take over established psychiatric practice. Expertise in acute hospital care and psychopharmacology is desired. Must be willing to work hard and to enjoy the beauty and fun of the Pacific Northwest. One hour from Seattle. Reply to Box 6387, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

DIAGNOSTIC RADIOLOGIST NEEDED IN IDAHO. Outstanding recreational area of Southern Idaho. Small hospital/office practice. Perfect for semi-retired physicians—about 30 hrs/wk work. Minimal call. Can join group of two other radiologists with good income potential and benefits. Need experienced general radiologist with ultrasound and nuclear medicine. No angiography, CT or interventional. Reply with CV to Magic Valley Radiology Associates, P.O. Box 2349, Twin Falls, ID 83301 or call (208) 734-0212.

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THE JAMES IRVINE CENTER for the Study of Leukemia and Lymphoma in the Division of Anatomic Pathology at the City of Hope National Medical Center, is seeking a well qualified academic immunopathologist who has completed a post-residency fellowship in immunopathology. The candidate should have extensive experience with immunological procedures with a demonstrated publication record. The appointee will be expected to initiate and conduct innovative basic research projects as part of a multidisciplinary approach for the study of human leukemias and lymphomas and should have the ability to interact with other investigators in areas of common research interest. Starting annual salary $45,000 or more depending on qualifications and experience. Send curriculum vitae to Henry Rappaport, MD, Chairman, Division of Anatomic Pathology, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010.

POSITIONS AVAILABLE for qualified physicians to form two to three man group to provide full time coverage at Urgent Care Clinic in Stockton, Calif. Must reside in Stockton area. Must be Board eligible or certified in Emergency Medicine or Family Practice. Generous salary and benefit package available. Contact R. Richard Goldman, MD, (209) 946-0383 or send CV to 2665 Westminster, Stockton, CA 95204.

DIRECTOR OF STUDENT HEALTH CENTER, Sonoma State University announces the opening for a Director of the Student Health Center. The University, a campus of the California State University system, is located 49 miles north of San Francisco and is a liberal arts and sciences institution. The Director, as well as administering a comprehensive outpatient medical clinic, shares with two other full-time physicians the medical care of approximately 6,000 students. A valid California Medical license is required at the time of employment, along with five years experience, excluding internship, in the practice of medicine, one of which must be administratively related. For complete job announcement, required qualifications and application procedures, please contact: Search Committee, Director, Student Health Center, c/o Personnel Office, Sonoma State University, Rohnert Park, CA 94928; (707) 664-2166. Salary Range. $53,472 to $64,740 annually. Application Deadline: November 1, 1983. AA/EO Employer.

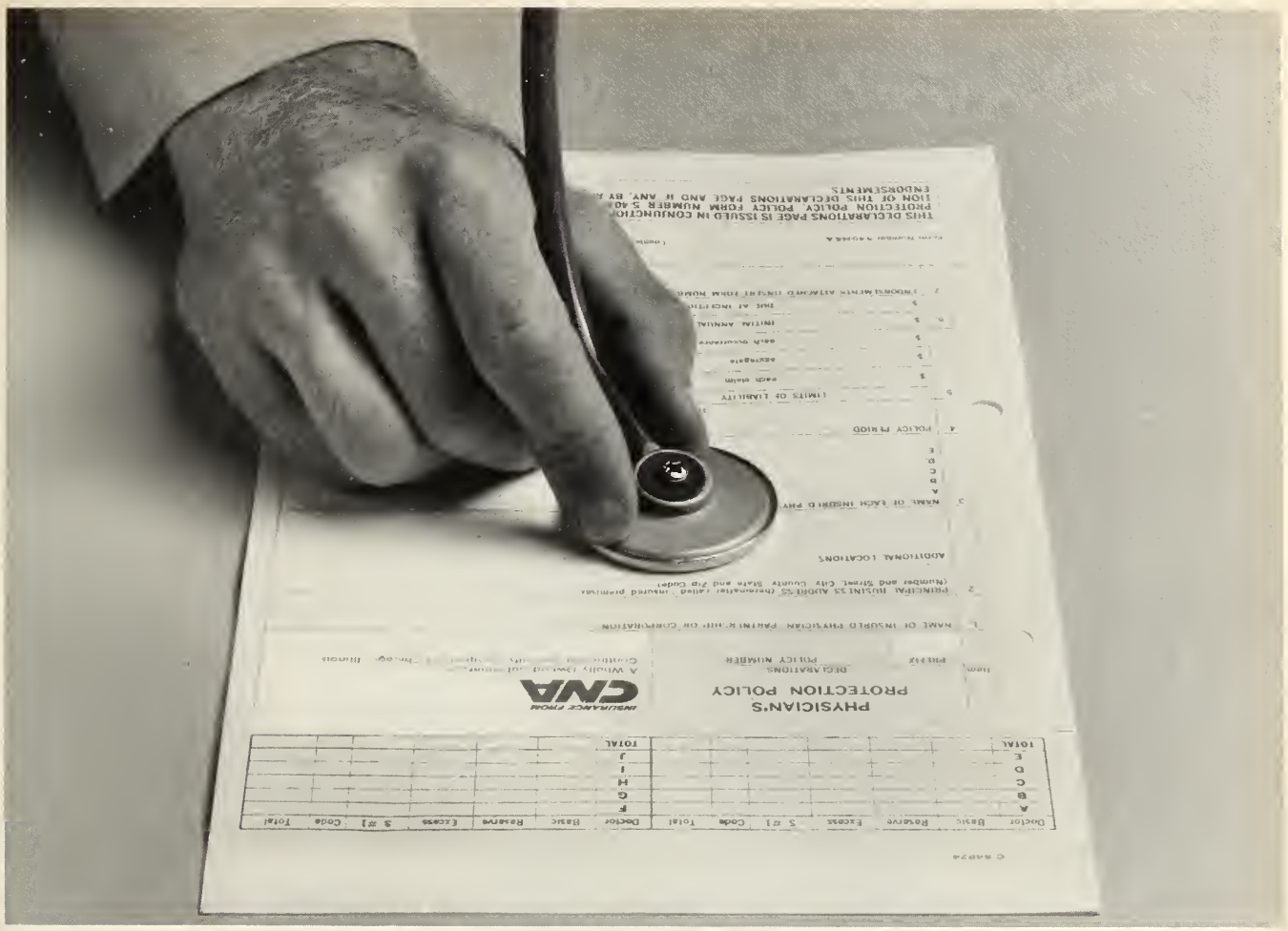
WASHINGTON STATE FAMILY PRACTICE— Young active medical community seeks Board certified or eligible Family Practitioners, to associate in economically stable community, 2 hrs. from Spokane, Wash. Liberal start-up incentives and comfortable call schedule make this an attractive opportunity. Modern clinic facility adjacent to well-equipped 28 bed rural hospital. Community situated on 2 huge lakes, providing unlimited water recreation, hunting, and skiing within 1 hr. Contact: Dr. Black at (509) 633-0127 or Steve Smith, Administrator, Coulee Comunity Hospital, Box H, Grand Coulee, WA 99133; (509) 633-1753.

GENERAL SURGEON—OB/GYN—FAMILY PRACTICE PHYSICIANS needed to affiliate with a small community hospital. Excellent opportunity for establishing a very lucrative practice. Send CV or call: Lynn E. Gair, MD, 2101 7th St., Wasco, CA 93280; (805) 758-2203.

CALIFORNIA—URGENT CARE. Positions available for Fall 1983 in freestanding, urgent care settings in several locations. Board certification or eligibility in Emergency Medicine, Family Practice, or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Avenue, Suite 500, Oakland, CA 94610; (415) 832-6400.

CALIFORNIA EMERGENCY DEPARTMENT DIRECTOR: wanted for moderate volume Emergency Unit in San Francisco. Annual salary $60,000+. Marketing experience/interest necessary. Send CV to: Emergency Physicians Medical Group, 1818 Union Street, San Francisco, CA 94123.

(Continued on Page 589)



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Cough or cold, there's a form of Citra Forte to help your patients *feel* better, as well as *get* better. And since Citra Forte Syrup and Capsules are both "prescription-only" your patients get the added assurance that comes with "doctor-only" medication.

Citra Forte is the "total" cough and cold remedy. The pleasant tasting syrup provides antitussive and antihistaminic action; while the convenient capsules are also antitussive and antihistaminic, with decongestant and analgesic activity to relieve cold symptoms.

There may be no "good" time for a cough or cold, but anytime a patient has either one is a good time for Citra Forte...syrup or capsules

CITRA® FORTE SYRUP

Each 5cc contains:

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg.
Ascorbic Acid	30 mg.
Pheniramine Maleate	2.5 mg.
Pyrilamine Maleate	3.33 mg.
Potassium Citrate	150 mg.

CITRA® FORTE CAPSULES

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg.
Ascorbic Acid	50 mg.
Pheniramine Maleate	6.25 mg.
Pyrilamine Maleate	8.33 mg.
Chlorpheniramine Maleate	1 mg.
Phenylephrine HCl	10 mg.
Salicylamide	227 mg.
Caffeine Alkaloid	30 mg.
Acetophenetidin	120 mg.

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.

CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism. WARNING: This preparation may damage the kidneys when used in large amounts or for a long period of time. Use with caution in greater than recommended dose or regularly for longer than 10 days (Acetophenetidin).

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(Continued from Page 468)

R. DiBartolomeo, MD, Secretary, 2420 Castillo St., Santa Barbara 93105.

January 11—**Endocrinology.** LLU. Wednesday. 4 hrs. $50.

January 11—**Diabetic Therapy in 1984.** LLU. Wednesday. $50.

January 16-20—**2nd Biannual Gastrointestinal and Hepatic Diseases Conference.** Honolulu Medical Group Research and Education Foundation at Mauna Kea Beach Hotel, Hawaii. Monday-Friday. 20 hrs. Contact: Yvonne Brewer, MPH, Education Director, HMGREF, 550 Beretania St., Honolulu, HI 96813. (808) 537-2211, ext. 751.

January 19-21—**American Society for Gastrointestinal Endoscopy Meeting** at San Francisco. Thursday-Saturday. 16 hrs. Contact: Mr. William T. Maloney, Executive Director, ASGE/PG, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** See Of Interest To All Physicians, January 20-22.

January 23-26—**Maui Coronary Heart Disease Course.** UCD at Maui, Hawaii. Monday-Thursday.

January 23-27—**8th Annual Hawaii Echocardiography Conference.** Honolulu Medical Group Research and Education Foundation at Kahala Hilton Hotel, Honolulu. Monday-Friday. Contact: Yvonne Brewer, MPH, Education Director, HMGREF, 550 S. Beretania St., Honolulu, HI 96813. (808) 517-2211, ext. 751.

January 26-28—**Alzheimer's Disease: Toward Clinical Management.** Annenberg Center for Health Sciences, Rancho Mirage. Thursday-Saturday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 340-3911.

January 30-February 2—**Current Concepts in Cardiology.** American College of Cardiology and Coronado Hospital at Hotel Del Coronado, Coronado. Monday-Thursday. Contact: Registration Secretary, Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

February 2-4—**Recent Advances in Geriatric Medicine: A New Look at Caring for the Elderly.** UCSD at Holiday Inn, San Diego. Thursday-Saturday.

February 8—**Diagnosis of Acute and Chronic Abdominal Pain.** LLU. Wednesday. 4 hrs. $50.

February 8-10—**17th Annual Recent Advances in Neurology.** UCSF at Fairmont, San Francisco. Wednesday-Friday.

February 13-24—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

February 16-18—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology and Orange Coast Heart Institute, Hoag Memorial Hospital Presby. at Newport Beach Marriott Hotel and Tennis Club, Newport Beach. Thursday-Saturday. Contact: Registration Secretary, Extramural Programs Department, ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

February 18—**Infectious Disease.** UCD at Red Lion Inn, Sacramento. Saturday.

February 20-23—**Office Endocrinology.** UCSF. Monday-Thursday.

February 29-March 3—**7th Annual Course: Immunology and Clinical Practice of Allergy.** UCSD. Wednesday-Saturday. 20 hrs.

OBSTETRICS AND GYNECOLOGY

October 17-22—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** UCI and Memorial Hospital Medical Center at Sheraton Newport, Newport Beach. Monday-Saturday. 48 hrs.

October 31-November 4—**13th Annual Review Course in Gynecology and Obstetrics.** USC at Pasadena Hilton Hotel, Pasadena. Monday-Friday.

November 5—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton, Pasadena. Saturday.

November 10-12—**2nd Annual Conference on Infantile Apnea & Home Monitoring of High Risk Infants.** Annenberg Center for Health Sciences and the Medical Center of Tarzana at Annenberg Center for Health Sciences, Rancho Mirage. Thursday-Saturday. 12 hrs. Contact: Annenberg Center for Health Sciences, Eisenhower Medical Ctr., 3900 Bob Hope Drive, Rancho Mirage 92270. (619) 340-3911 X1661.

December 2-4—**Current Issues in Perinatal Medicine.** UCI and Memorial Hospital Medical Center at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. 15 hrs.

December 9-10—**Genetics, Birth Defects and the High Risk Patient.** UCD at Capitol Plaza, Sacramento. Friday-Saturday.

January 9-10—**Advanced Fetal Heart Rate Monitoring.** Memorial Hospital Medical Center and UCI at Hyatt Regency, Long Beach. Monday-Tuesday. 10 hrs. Contact: Memorial Hospital Medical Center, Asst. Director, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801-1428.

February 5-10—**Ob/Gyn Update: 1984.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 11-12—**Los Angeles Ob/Gyn Forum.** Los Angeles Ob/Gyn Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. 10 hrs. $80. Contact: Director of Medical Education, LA Ob/Gyn Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 13-17—**39th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Director of Medical Education, Ob/Gyn Assembly of S. California, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 16-18—**Advanced Fetal Heart Rate Monitoring.** Memorial Hospital Medical Center and UCI at Sheraton-Waikiki, Oahu. Thursday-Saturday. 10 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801-1428.

PEDIATRICS

October 22-27—**American Academy of Pediatrics Scientific Meeting** at Moscone Center, San Francisco. Sunday-Thursday. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60204.

October 24-29—**Allergy and Immune Diseases in Children.** Symposium Maui, Inc., Hawaii Chapter American Academy of Family Practice and Hawaii Medical Association at Kapalua Bay Hotel, Maui. Monday-Saturday. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, Hawaii 96761.

October 29-November 5—**8th Annual Pediatrics for the Practitioner.** UCI and Memorial Hospital Medical Center at Mauna Kea Beach Hotel, Hawaii. One week. 20 hrs.

November 10-12—**2nd Annual Conference on Infantile Apnea and Home Monitoring of High Risk Infants.** See Obstetrics and Gynecology, November 10-12.

November 12—**25th Annual Pediatric Symposium.** Southern California Permanente Medical Group at Newport Marriott Hotel, Newport Beach. Saturday. Contact: Dana Reisman, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

November 18-19—**Childhood Diabetes: New Changes in Care.** UCD at Woodlake Inn, Sacramento. Friday-Saturday. $95.

November 18-21—**5th Annual Las Vegas Seminar—Pediatrics Update.** American Academy of Pediatrics at Caesar's Palace, Las Vegas. Friday-Monday. Contact: Eve Black, Executive Secretary, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

December 3—**Management of the Critically Ill Child.** California Chapter 1 of American Academy of Pediatrics at Holiday Inn, San Francisco. Saturday. Contact: Beverly Busher, 1125 A St., Ste. 210, San Rafael 94901. (415) 459-4775.

January 11—**23rd Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at Los Angeles. Wednesday. Contact: Eve Black, Executive Secretary, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. One week. 21 hrs. $335.

January 27-29—**22nd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 27-29.

PSYCHIATRY

October 21-22—**Family Violence and Violent Interactions.** Mental Research Institute, Palo Alto. Friday-Saturday. 6 hrs. $85. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 22-29—**Nonverbal Expression of Self.** UCSF at Kauai Surf Resort, Kauai, Hawaii. One week. 33 hrs. $350 individuals, $600 couples.

October 24-26—**Basic Hypnotherapy: Principles and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $65. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 24-28—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $175. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 26-30—**American Academy of Child Psychiatry.** San Francisco. Wednesday-Sunday. Contact: V. Q. Rausch, 1424 16th St., NW, Ste. 201A, Washington, DC 20036.

October 29—**The Interactional View.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 5—**Treating Depression in a Marital Context.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $60. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 5-12—**Difficult Patients in Medical Practice.** UCI Dept. of Psychiatry on Caribbean Cruise aboard the Sun Princess. Contact: Leslea Miller, 2000 Quail St., Newport Beach 92660. (714) 751-3024.

November 11-13—**29th Annual Group Therapy.** UCSF at Holiday Inn Bay Bridge, Berkeley. Friday-Sunday.

November 12—**Family Interactions and Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $95. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 14-18—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 20 hrs. $195. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 18-19—**Family Therapy Training and Supervision: Creating Contexts of Competence.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

December 19-24—**Conference on Psychiatric Care of the Injured Worker.** Pacific Medical Center at SS Constitution, San Francisco to Honolulu. Monday-Saturday. 30 hrs. $465. Contact: Robert B. Cahan, MA, MD, Program Director, 2340 Sutter St., Ste. 308, San Francisco 94115. (415) 587-7973.

January 14—**The Interactional View.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 16-19—**Family Crises: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 21—**Developing a Personal Evolving Model of Therapy:**

(Continued on Page 572)

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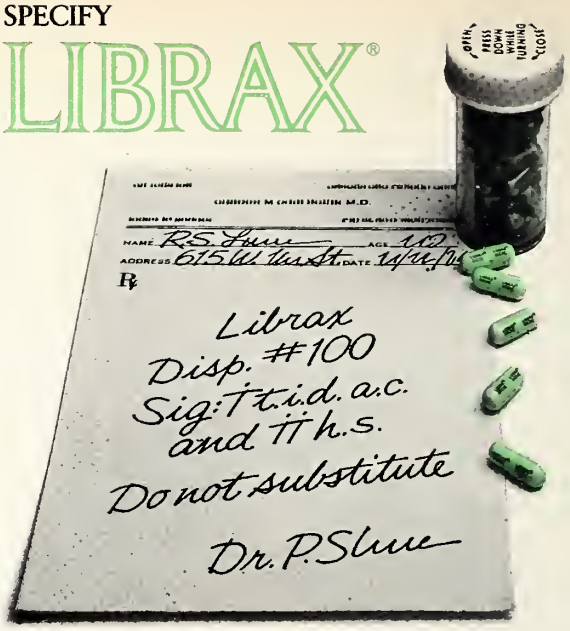

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Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

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As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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Influenza Vaccination and Theophylline Pharmacokinetics in Patients With Chronic Obstructive Lung Disease

BARRY M. STULTS, MD, *and* PETER A. HASHISAKI, MD, *Salt Lake City*

Total theophylline clearance rate was measured before and 24 hours after standard influenza vaccination in seven men with stable chronic obstructive lung disease. In four, total theophylline clearance rate was also measured 48 hours after vaccine administration. There was no significant change in the clearance rate after either time interval. These results do not support recent recommendations to monitor serum theophylline concentrations or reduce theophylline dosage during the 48-hour period following influenza vaccination. Nevertheless, pending further studies, patients maintained on a regimen of theophylline preparations should be followed clinically for theophylline toxicity for the first several days after receiving influenza vaccine.

Elimination of theophylline from the body occurs predominantly via oxidative metabolism by hepatic cytochrome P-450 microsomal enzyme systems.[1,2] Multiple factors are known to alter hepatic theophylline metabolism and thereby change steady-state serum theophylline concentration.[3] Certain acute viral infections of the upper respiratory tract may transiently depress the hepatic elimination of theophylline, leading to a toxic reaction in some patients.[4-8] This observation is consistent with previous investigations showing that a variety of agents that activate the immune system and stimulate interferon synthesis may also simultaneously depress cytochrome P-450-linked monooxygenase systems that metabolize drugs in the liver.[6,9-14]

Standard influenza vaccination has recently been reported to significantly impair the elimination of theophylline and certain other drugs metabolized in the liver.[15-17] Other investigations have not confirmed these observations, however.[18-20] Annual influenza vaccination is recommended for patients who have chronic obstructive lung disease,[21] many of whom receive maintenance theophylline therapy. It is therefore important to determine whether or not influenza vaccination adversely affects theophylline pharmacokinetics. We have investigated the effect of influenza vaccination on theophylline clearance rate in clinically stable persons who have chronic obstructive lung disease 24 and 48 hours following vaccination. Serum interferon levels were measured before and after vaccination to determine their relationship to any observed interaction.

Patients and Methods

Seven men were electively admitted to either the Salt Lake City Veterans Administration Medical Center or the Clinical Research Center of the University of Utah. The mean age of the men was 64 years (range, 57 to 79). All had chronic bronchitis as defined clinically by the American Thoracic Society[22] and chronic airflow obstruction according to standard spirometric criteria.[23] Five of the men were currently smokers (5 to 30 cigarettes per day) and two were ex-smokers who had not smoked during the past year. Before the study, all had been receiving maintenance theophylline therapy by mouth on a long-term basis. None were receiving corticosteroids either by inhalation or by mouth. Other routine drug therapy was continued during the study period.

Two persons had received influenza vaccine a year before the study. Three others had received influenza

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vaccine two, three and five years before the study, respectively. The remaining two persons had never been vaccinated for influenza. Subjects were admitted to the study only after they met the following criteria designed to assure clinical stability and to eliminate those factors known to alter theophylline elimination:[3]

- No clinical deterioration of their chronic obstructive lung disease, including upper and lower respiratory tract infections, in the two months before the study.
- No clinical evidence of right or left ventricular congestive heart failure.
- No intake of medications known to affect theophylline elimination (erythromycin, β-blocking medicines, cimetidine, allopurinol or phenobarbital). The only exception was a patient who had been taking cimetidine, 300 mg by mouth at bedtime, for the past year; this regimen was continued during the study.
- No biochemical evidence of active liver disease.

They were asked to maintain their usual caffeine intake and dietary habits. Informed written consent was obtained from each subject after the study had been fully explained in a manner approved by the Human Studies Committee of the Salt Lake City VA Medical Center and the Institutional Review Board of the University of Utah School of Medicine.

Study Design

Maintenance oral theophylline therapy was discontinued on the first day of the study period. A constant intravenous infusion of aminophylline ([formerly theophylline ethylenediamine] 85% anhydrous theophylline, GD Searle & Company, Chicago) was then administered via infusion pump (IMED 922, IMED Corporation, San Diego, Calif) for the duration of the study. The concentration of the aminophylline infusion was calculated such that during the 24-hour period the subject received his usual total 24-hour dose of anhydrous theophylline in 1,500 ml of 5% dextrose in water. Total theophylline clearance rate (TTCR) was calculated according to the equation[24,25]

$$\text{TTCR (ml/min)} = \frac{Q}{C_{ss}} \times \frac{1{,}000}{60}$$

where Q = rate of theophylline infusion (mg per hr) and C_{ss} = steady-state serum theophylline concentration (μg per ml). Steady-state with respect to serum theophylline concentration was accepted when serum theophylline concentrations, measured 24, 25 and 26 hours after an intervention—that is, initiation of intravenous aminophylline infusion and administration of influenza vaccine—were within 1 to 2 μg per ml of each other and showed no consistent upward or downward change in the three serial samples.[25] In the average person, the mean difference among the three serially measured theophylline concentrations was 0.48 μg per ml. C_{ss} was calculated as the mean of the three samples.

After baseline total theophylline clearance rate was determined, each person received intramuscularly an injection of 0.5 ml of inactivated subvirion trivalent influenza vaccine (Wyeth Laboratories, Philadelphia; lot 212001; expiration date June 1982). The intravenous aminophylline infusion was continued and the total theophylline clearance rate was measured 24 hours after the vaccination in the seven men. In four, the total theophylline clearance rate was also determined 48 hours following administration of the influenza vaccine. Patients were monitored for vital signs and clinical theophylline toxic reaction every eight hours during the course of the study period.

TABLE 1.—*Total Theophylline Clearance Rate (TTCR) Before and 24 Hours After Influenza Vaccination in Seven Men With Chronic Obstructive Lung Disease*

Subject	Age (years)	Aminophylline Infusion Rate (mg/kg/24 hr)	Prevaccination TTCR (ml/kg/min)	24 Hour Postvaccination TTCR (ml/kg/min)	Difference in TTCR (ml/kg/min)
1	59	21.6	1.2	1.7	−0.5
2	61	18.2	1.3	1.0	0.3
3	69	20.0	1.8	1.8	0.0
4	60	13.2	1.3	1.2	0.1
5	61	11.3	0.8	0.7	0.1
6	57	12.8	1.1	1.3	−0.2
7	79	22.0	0.7	0.7	0.0
Mean	64	17.0	1.2	1.2	−0.03
SD	8	4.5	0.4	0.4	0.26

SD = standard deviation

Theophylline assay was done using the quantitative Enzyme-Mediated Immunoassay Technique (EMIT; Syva Inc, Palo Alto, Calif).[26] In our laboratory, the measurement of serum theophylline concentration has a coefficient of variation of ±3.0% at serum theophylline concentrations of 5 to 15 μg per ml.

Serum interferon titers were measured immediately before influenza vaccination and repeated at intervals of 8, 16, 24 and 48 hours and 7 to 10 days following vaccination. An automated, quantitative cytopathic-effect reduction assay for interferon was used.[27] The interferon titer was recorded as the reciprocal of the dilution producing 50% reduction in encephalomyocarditis virus cytopathic effect formed in the microassay system. The National Institutes of Health human leukocyte interferon standard (6023-901-527) with a reported titer of 20,000 units has an average titer of 23,000 units in the automated assay.*

Student paired *t* test was used to examine differences in the total theophylline clearance rate, serum theophylline concentration and interferon titers before and after influenza vaccination of each subject. For all statistical testing, *P* less than .05 was used as the minimal level of significance.

Results

The mean prevaccination total theophylline clearance rate for subjects 1 to 7 was 1.2 ± 0.4 ml per kg of body weight per minute (mean ± SD; Table 1); mean steady-state serum theophylline concentration was 9.0 ± 3.9 μg per ml (mean ± SD). The mean difference

*Jon Green, MD, Division of Infectious Diseases, performed the interferon assays.

TABLE 2.—*Total Theophylline Clearance Rate (TTCR) Before and 48 Hours After Influenza Vaccination in Four of Seven Men in Study*

Subject	Age (years)	Aminophylline Infusion Rate (mg/kg/24 hr)	Prevaccination TTCR (ml/kg/min)	48 Hour Postvaccination TTCR (ml/kg/min)	Difference in TTCR (ml/kg/min)
4	60	13.2	1.3	1.1	0.2
5	61	11.3	0.8	0.7	0.1
6	57	12.8	1.1	1.3	−0.2
7	79	22.0	0.7	0.7	0.0
Mean	64	14.8	1.0	1.0	0.03
SD	10	4.9	0.3	0.3	0.17

SD = standard deviation

in the total theophylline clearance rate before and 24 hours following influenza vaccination was -0.03 ± 0.26 ml per kg per minute (SD), which is not significant (paired t test, $P = .778$). Similarly, the mean difference in total theophylline clearance rate before and 48 hours after influenza vaccination in subjects 4 to 7 was not significant (0.03 ± 0.17 ml per kg per minute [SD], $P = .789$; Table 2).

Serum interferon was not detected in any of the seven persons before influenza vaccination or at intervals of 8, 16, 24 and 48 hours and 7 to 10 days following vaccination.

No adverse reactions to influenza vaccination or theophylline infusion were encountered during the study.

Discussion

A variety of agents that activate the immune system simultaneously depress drug-metabolizing, cytochrome P-450-linked monooxygenase systems in the liver.[6,9-14] As a result, these agents may have the potential to alter the therapeutic and toxic activities of certain drugs metabolized by the liver. The agents, which include certain acute infections (viral, bacterial and parasitic), vaccinations (pertussis and bacille Calmette Guérin) and synthetic polynucleotides, all have in common the ability to induce production of interferon. The passive transfer of interferon may depress hepatic cytochrome P-450 drug metabolism in experimental animals.[12] Based on these findings, it has been hypothesized that interferon production may contribute significantly to the observed depression of drug metabolism in these studies, though other immune mechanisms may also play important roles.[6]

Theophylline elimination occurs largely via oxidative metabolism in hepatic cytochrome P-450 systems.[1,2] Recent investigations suggest that some infections and other types of immune stimulation may depress theophylline elimination.[4-8,15,16] Certain respiratory tract viral infections have been shown to acutely prolong plasma theophylline half-life by 68% in one study (influenza A and adenovirus)[4] and to increase serum theophylline concentration by a mean of 16.5 μg per ml in another study (influenza B).[5]

Standard influenza vaccination with inactivated vaccine has also been reported to decrease the elimination of theophylline and the hepatically metabolized drug, aminopyrine.[6,15-17] In four healthy volunteers, Renton and co-workers found a mean 51% reduction in serum theophylline clearance 24 hours following inactivated whole virion influenza vaccination. They also measured serum theophylline concentrations before and after influenza vaccination in three patients with chronic obstructive lung disease and found increases of 219%, 89% and 85%, respectively, within 12 to 24 hours of vaccination.[6,15] Walker and associates reported the case of a pediatric patient who had a 70% increase in serum theophylline concentration five hours following subvirion influenza vaccination.[16] Similarly, in another recent study hepatic metabolism of aminopyrine was reduced by a mean 46% a week following influenza vaccination in healthy volunteers.[17] On the basis of these reports, some authorities have suggested that consideration be given to omitting or decreasing theophylline dosage for 24 hours following influenza vaccination.[28]

The present investigation does not confirm a clinically significant effect of influenza vaccination on theophylline elimination. In seven elderly men with chronic obstructive lung disease, we found no alteration in total theophylline clearance rate 24 hours following influenza vaccination. In four of these persons, there was also no change in total theophylline clearance rate 48 hours after administration of the vaccine. Three additional investigations reached a similar conclusion.[18-20] However, these studies are limited by their use of sustained-release theophylline preparations and measurement of isolated serum theophylline concentrations rather than theophylline elimination values. There may be great dose-to-dose intrasubject variation in the absorption profile of sustained-release theophylline medicines.[29] This results in considerable dose-to-dose variability in serum theophylline concentrations measured at a given interval following theophylline ingestion. Still, in 12 clinically stable asthmatic adults receiving oral maintenance therapy with a sustained-release theophylline preparation, Fischer and colleagues noted no significant increase in serum theophylline concentration 24 hours, 72 hours and one and two weeks following influenza vaccination.[20] A single subject in this study did show a 10 μg per ml increment in serum theophylline concentration 24 hours after vaccination associated with symptoms of toxic reaction to theophylline. The other two preliminary studies found no significant change in serum theophylline concentration 24 hours following influenza vaccination in a total of 16 persons with stable chronic obstructive lung disease.[18,19]

There are several possible explanations for the disparate results of these studies. First, different preparations of standard, inactivated vaccine may exert maximal effects on hepatic drug metabolism at different times.[30] The preparations used by Renton and Walker and co-workers[15,16] impaired theophylline elimination within 24 to 36 hours of vaccination, whereas the preparation used by Kramer and McClain[17] did not exert its maximum effect on aminopyrine metabolism

until seven days after vaccination. Against this hypothesis, Fischer and associates found no significant change in serum theophylline concentration up to 14 days after influenza vaccination.[20]

Another consideration is that only certain influenza vaccine preparations may be capable of inducing the synthesis of circulating interferon or of depressing hepatic drug metabolism, or both.[30] The inactivated influenza vaccine preparation used in this study did not induce production of measurable serum interferon at postvaccination intervals of 8, 16, 24 and 48 hours and 7 to 10 days. It is not clear, however, that interferon production is the mechanism by which inactivated influenza vaccine may depress the elimination of some hepatically metabolized drugs. Inactivated influenza vaccine is not likely to be a potent inducer of interferon production, which may require active influenza virus replication.[31-36]

Differences in study population also do not obviously explain the disparate results of the available studies of influenza vaccination and theophylline elimination. Age is apparently not a confounding variable, as studies reporting a depressant effect of influenza vaccination on theophylline elimination have included both younger[16,17] and older persons,[15] as have studies showing no effect.[18-20] Cigarette smoking also does not appear to be a significant factor. Five of seven persons in our study were smokers, whereas all of the subjects in the study by Fischer and colleagues[20] were nonsmokers. Neither study found an effect of influenza vaccination on theophylline elimination. Prior exposure to influenza vaccination does not seem to condition who will or will not have depressed theophylline elimination following vaccination. Two of our subjects had not previously received influenza vaccine, whereas the other five had been vaccinated within the past five years. Neither group showed a decrease in theophylline elimination.

Available studies do not support current recommendations to either monitor serum theophylline concentrations or omit or decrease theophylline dosage for the 24 to 48 hours following trivalent influenza vaccination.[28] In the absence of definitive information, vaccinated patients should be advised to report symptoms suggestive of toxic reaction to theophylline immediately to their physicians. Further studies are warranted to determine the frequency with which influenza vaccination may depress hepatic drug elimination as well as the timing, mechanism and conditioning factors for this interaction.

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Fecal Excretion of Soluble Magnesium by Humans

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To test the hypothesis that fecal magnesium excretion is related to fecal volume, fecal specimens were collected from healthy persons who drank 32 single doses of poorly absorbed carbohydrate (mannitol, lactulose or raffinose): the concentration of Mg^{++} (Y) in fecal water (X) was linearly and inversely related to fecal volume—that is, $Y = 42 - 0.03\ X$. In contrast, after drinking magnesium sulfate, the concentration of Mg^{++} in fecal water rose and, except after the lowest ingested dose of 10 mmol, the points relating Mg^{++} concentration and fecal volume were outside the upper 95% confidence limit of the linear regression line. These findings could be useful when physicians are analyzing stool specimens for supportive evidence of magnesium misuse in baffling cases of diarrhea.

Magnesium is poorly absorbed from the gastrointestinal tract.[1-3] Soluble salts of Mg^{++}, therefore, will obligate retention of water in the intestinal lumen and will thereby increase ileostomy and fecal output.[4]

Magnesium hydroxide, magnesium citrate and magnesium sulfate are laxatives that may be misused by patients who then present with puzzling diarrhea. Measurement of Mg^{++} concentration in fecal water is used to prove a diagnosis of Mg^{++} abuse.[5] Yet Mg^{++} is present normally in fecal water, and the fecal concentration of Mg^{++} might vary with fecal volume. We report our findings on the relationship between Mg^{++} concentration and fecal volume when diarrhea is induced by poorly absorbed carbohydrate. These data should prove useful to physicians who are analyzing stool specimens for evidence of Mg^{++} misuse.

Methods

Details of materials and methods have been published elsewhere.[6] This study was approved by the Human Subjects Committee of the University of Washington, Seattle, and of the Dunn Clinical Nutrition Unit, Cambridge, United Kingdom. Healthy volunteers drank, instead of breakfast, a solution containing a dose of a poorly absorbed solute. They were asked to try to defecate beforehand; thereafter, all stool specimens for 48 hours were collected in plastic bags over solid carbon dioxide while they continued their usual diet and activities. At least one week intervened between experiments. In all, 14 doses of mannitol, 38 to 357 mmol, were given to two subjects; 12 doses of lactulose, 30 to 245 mmol, were drunk by two subjects, and 6 doses of raffinose, 29 to 144 mmol, were drunk by one subject. One person ingested six doses of magnesium sulfate, 10 to 73 mmol.

Frozen fecal specimens were weighed, thawed and blended. To measure the extracellular water content, 30 grams of blended stool were mixed with 0.5 ml (2 μCi) of (carbon 14) polyethylene glycol 4,000 (PEG, 30 grams per dl); the mixture was spun for 900,000 g • minutes at 5°C. After centrifuging, the ^{14}C in 0.2-ml portions of supernate were counted so that the proportion of extracellular water in stool could be determined from the following relationship:

^{14}C per ml when ^{14}C PEG was added to 30 grams of water divided by the
^{14}C per ml when ^{14}C PEG was added to 30 grams of stool, and the resulting ratio

was then multiplied by the total weight of the stool specimen. Polyethylene glycol is an appropriate marker of fecal extracellular water because it remains in the fecal supernate and not with the fecal sediment.[7]

One volume of fecal water was diluted up to 20 volumes with nitric acid and deionized water. Magnesium and calcium in diluted fecal water were measured by atomic absorption spectrometry.

Results

The concentration of Mg^{++} in fecal water fell as stool volume increased when diarrhea was induced by

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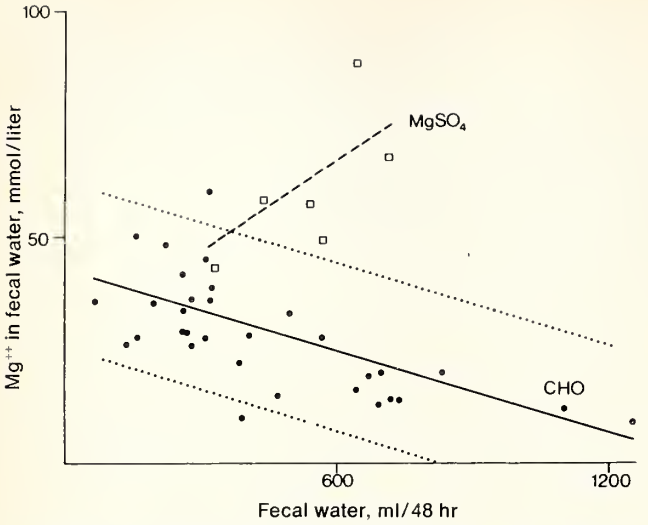

Figure 1.—Relationship between Mg^{++} concentration (mmol per liter) and fecal water (ml per 48 hours). ● = stools after single doses of poorly absorbed carbohydrate (28 to 357 mmol). $Y = 42 - 0.03\ X$. The 95% confidence limit for individual Y values[8] is ±19. □ = stools after single doses of magnesium sulfate ($MgSO_4$) (10 to 73 mmol); the interrupted line refers to the regression line of the data from $MgSO_4$ experiments.

poorly absorbed carbohydrate. This relationship was described as

$$Y = 42 - 0.03\ X\ (r = 0.68)$$

where Y is Mg^{++} in mmol per liter and X is fecal water output in ml per 48 hours (Figure 1). Total output of Mg^{++} in fecal water was 11±4 mmol in 48 hours (mean±SD, N = 32, range 2.4 to 19.2). The 95% confidence limits for individual Y values[8] is given by $(t)\ S_{yx}$ which is (2.04) 9.43 or ±19 (Figure 1).

By contrast, when diarrhea was induced by magnesium sulfate, the concentration of Mg^{++} in fecal water rose as fecal volume increased:

$$Y = 17 + 0.08\ X\ (r = 0.69).$$

All these points were outside the 95% confidence limits established from $Y = 42 - 0.03\ X$ (Figure 1), except for the stool production of 336 grams per 48 hours that followed the ingestion of the lowest dose, 10 mmol of magnesium sulfate. The concentration (mmol per liter) of Mg^{++} correlated with the millimoles of magnesium sulfate ingested: $Y = 37 + 0.63\ X\ (r = 0.89)$.

Fecal calcium (Ca^{++}) was measured because its concentration, after poorly absorbed carbohydrate, should have a similar relation to fecal volume as did Mg^{++}. In fact, fecal Ca^{++} concentration proved also to be inversely related to fecal volume ($Y = 21 - 0.01$ X, where X is ml of fecal water in 48 hours). Contrasting with fecal Mg^{++}, however, fecal Ca^{++} concentration fell ($Y = 20.5 - 0.014$ X) when diarrhea was induced by magnesium sulfate.

Discussion

These findings indicate that the fecal concentration of soluble Mg^{++} is inversely related to the fecal volume when healthy persons eating a Western diet ingest single doses of poorly absorbed carbohydrate. This relationship is not surprising; 5 to 20 mmol of Mg^{++} are ingested each day normally, and about two thirds is excreted in the stools.[1-3] Most of the Mg^{++} in feces is of exogenous origin; gastric, pancreatic and biliary secretions contain about 1 mmol per liter of Mg^{++}.[1,2] Therefore, the concentration of Mg^{++} in fecal water will depend on the extent to which exogenous Mg^{++} in the intestinal lumen is flushed out, on the diluting volume of fecal water and on the aqueous solubility of the fecal magnesium salts. Our values for fecal Mg^{++} concentration may be higher than those in patients who have chronic diarrhea. Fecal magnesium concentration ranged from 0.1 to 11.3 mmol per liter in 19 patients with chronic diarrhea not due to surreptitious laxative ingestion.[5] Fecal volumes were not specified and diets were not mentioned, so comparison with our data is difficult.

Among cases of intractable diarrhea referred to gastroenterologists, abuse of laxatives is a major etiologic consideration.[9] Might our findings be useful in helping with the diagnosis of those patients who are abusing magnesium salts? The methods that were used in the present study are somewhat impractical for the usual clinical situation where it is difficult to collect stool specimens for 48 hours and to quantify fecal extracellular water by measuring the distribution of ^{14}C polyethylene glycol. If a fecal specimen were predominantly—that is, more than 80%—water, the minor contribution of fecal solids to fecal volume could be ignored. The stools after administration of poorly absorbed carbohydrate that consisted of more than 80% water were those that could be mixed and readily poured into centrifuge tubes; the extracellular water content of these stool specimens was more than 400 ml in 48 hours. In Figure 1 it can be seen that there were 15 such specimens. The maximum concentration of Mg^{++} in the fecal water of these 15 stools was 34 mmol per liter. Therefore, a fecal Mg^{++} concentration greater than 34 mmol per liter in the supernate of a random sample of a patient's watery stool would be highly suggestive of magnesium abuse. Other corroborative evidence would be the gap between the osmolality of the fecal water and twice the sum of the sodium and potassium concentrations.[5]

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Comparison of Two Therapeutic Regimens Using the Same Topical Corticoid for Stable Psoriasis

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In a masked, randomized, concurrently controlled clinical trial we compared the therapeutic response of two regimens in which the same topical corticoid was used to treat 52 men who had stable psoriasis. One regimen, called reduced dose, *consisted of once-a-day application of a representative potent fluorinated topical steroid ointment, fluocinonide (Lidex), combined with three-times-a-day application of its vehicle. The other regimen, called* traditional dose, *consisted of four-times-a-day topical application of the same steroid. Patients were assigned to one of the two regimens and observed for six weeks. Confidence intervals for the difference in true mean response under these two regimens provide good evidence that for these patients the traditional dose was not clinically superior to the reduced dose.*

Of the almost 13 million persons in the United States who suffer from one or more types of chronic steroid-responsive dermatosis that include eczema, seborrhea and psoriasis, more than 1 million have psoriasis.[1] The development of topical anti-inflammatory corticosteroids in the early 1950s and the subsequent development of the more potent and more expensive fluorinated corticoid derivatives were major advances in the treatment of these conditions. Individual drug companies' recommendations of multiple applications a day of topical corticoids by patients with steroid-responsive dermatosis have become accepted medical practice. Little work has been done, however, to verify the need for several applications a day.[2-4] A considerable saving in medication costs, possible reductions in adverse side effects and improved compliance could be realized if less frequent applications were as effective as the recommended several applications a day.

To investigate the need for several applications a day of topical steroids for the treatment of steroid-responsive dermatosis, we selected a common form, psoriasis, and the most commonly prescribed of the fluorinated topical corticoids, fluocinonide (Lidex).[5] Fluocinonide has been proved effective in the treatment of psoriasis.[6-9] We conducted a masked, randomized, concurrently controlled clinical trial using Lidex ointment in ambulatory patients with stable psoriasis to assess the difference between the therapeutic responses to the traditional dose of four-times-a-day unoccluded applications and to a reduced dose of once-a-day (at bedtime) unoccluded application of the active compound plus three-times-a-day unoccluded applications of its vehicle.

Methods

Size of the Study

Sample size calculations indicated that 25 subjects should be assigned to each therapeutic regimen in order to be 97.5% sure that a true mean therapeutic difference of one unit (see Table 1) would lead to an

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observed mean difference statistically significant at the two-sided 5% level. It was decided to enroll 55 rather than 50 patients to allow for possible dropouts. The planning estimate for variance of therapeutic outcomes was obtained from the composite judgment of three experienced dermatologists, each of whom made an independent forecast of the distribution of therapeutic responses of 100 psoriatic patients receiving the traditional dose of fluocinonide ointment over a period of six weeks.

Patient Selection

The study was conducted at the San Francisco Veterans Administration Medical Center. After the study had been approved, all patients presenting to the Dermatology Clinic who met the specific criteria were invited to participate. This continued until the desired sample size of 55 was reached.

Patients who had classical stable psoriasis vulgaris, with lesions limited to the extremities, trunk or scalp, were considered eligible for inclusion. Those with the uncommon pustular variant were excluded, as were patients with palm, sole or extensive facial or groin lesions, because variation in skin thickness in these body areas produces a variable response to topical steroid therapy. Patients who had received systemic corticosteroids or methotrexate during the three months before the study were also excluded. However, psoriatic patients who had recently had topical steroid or tar therapy were not excluded. All alternative treatments were discontinued for patients who entered the study. In all, 55 patients who met the criteria for the study agreed to participate.

Stratification of Patients

After informed consent was obtained, the principal investigator (T.P.S.) used the following criteria to assign the 55 eligible patients to one of three severity categories based on the extent of their psoriatic lesions:

1. *Mild.* Lesions limited to the elbows or knees, or the presence of fewer than ten small (less than 1 cm in diameter) scattered plaques (35 patients).

2. *Moderate.* More than ten scattered lesions affecting no more than 50% of the body's surface area (18 patients).

3. *Severe.* Lesions covering more than 50% of the body's surface area (two patients).

Assignment to Treatment

In each severity category the first patient was assigned to either the traditional-dose or the reduced-dose regimen at random. Then subsequent patients in each category were alternately assigned to one of the two regimens. Patient assignments were managed by a research assistant who also supplied patients with the appropriate medicine. The principal investigator, who entered patients into the study, was unaware of the patient allocation schema and, by the use of masking, did not know the history of prior treatment assignments.

TABLE 1.—*Therapeutic Outcome*

Change in Psoriatic Lesions—7-Point Scale	
−3	Much more scale or much more erythema, or both
−2	Somewhat more scale or somewhat more erythema, or both
−1	More scale or more erythema, or both
0	No difference in scale or erythema
+1	Less scale or less erythema, or both
+2	Much less scale or much less erythema, or both
+3	Clear (may have residual erythema)

Masking

At the start of the six-week trial, the research assistant gave each patient two 60-gram tubes, identical in appearance. Patients assigned to the reduced-dose group received one tube containing fluocinonide that bore instructions to apply at bedtime, and a second tube containing the drug vehicle that bore instructions to apply three times a day. The contents of the two tubes were indistinguishable. Patients assigned to the traditional-dose group received two tubes, both containing fluocinonide, one marked to apply three times a day and the other marked to apply at bedtime. Patients who had more extensive involvement were given additional tubes following the preceding schema. Neither the principal investigator nor the patients knew which compound the tubes contained.*

Patient Follow-up and Dropouts

Patients were seen weekly by the principal investigator and the research assistant. During the period of the trial, they received all of their dermatologic care from the principal investigator.

Three patients failed to complete the study. One traditional-dose patient in the mild category was dropped after two weeks because of an exacerbation of his disease that required admission to hospital; one reduced-dose patient in the moderate category did not return after his first visit and was lost to follow-up; one reduced-dose patient in the moderate category dropped out after two weeks because the time involved in the trial conflicted with the requirements of his new job. Of the 52 patients who completed the study, 34 were classified as mild (17 in the traditional-dose group, 17 in the reduced-dose group), 16 as moderate (9 traditional dose, 7 reduced dose) and 2 as severe (one in each group).

Compliance

Two methods were used to enhance patients' compliance with the treatment regimens. Patients were asked to keep a home diary in which they recorded the time they applied the drug and the length of time each application took. At the time of their weekly visits, the

*Syntex Laboratories, Inc, Palo Alto, Calif, supplied the tubes of drug and vehicle.

research assistant collected the diaries and issued new ones. Patients were also asked to bring in their tubes at each visit and give them to the research assistant, who collected the empty tubes and issued new ones. If the tubes were not empty, he weighed them to determine the amounts used and returned them to the patients.

Clinical Observations

Judgments about clinical response over a period of time that are based on memory or progress notes may be unreliable. To avoid this problem, we used color photographs of patients' lesions. Although this method poses difficulties in evaluating the induration or elevation of psoriatic plaques, we felt that the benefits gained from the use of color photographs—in terms of increased reliability of clinical judgment—outweighed this limitation.

The research assistant took color photographs of the psoriatic lesions of each patient at the start of the trial, after two weeks and after six weeks. Color print photographs were taken with a 35-mm single-lens reflex camera. Photoflood lighting was used to enhance and standardize the quality of the photographs. The distance at which each photograph was taken was recorded to ensure that all photographs of each patient were taken at the same distance. The 3½-in by 5-in photographs were mounted in pairs, with the "before" photograph on the left and either a "two-week" or a "six-week" photograph on the right.

Three dermatologists, including the principal investigator, evaluated the resulting 104 pairs of photographs. All of these evaluations were masked with respect to treatment assignment. First, the 104 pairs of photographs were presented in random order to each of the three dermatologists, who made independent judgments of changes in the lesions depicted, using the seven-point scale of Table 1. This review familiarized them with the range and type of therapeutic responses. One week later this process was repeated with the 104 pairs of photographs in a different random order. This second set of judgments was used for analysis because the dermatologists were more familiar with the evaluation scale the second time they were asked to view the photographs.

In addition to the judgments of the dermatologists, each patient evaluated the effect of his treatment regimen. After two weeks and after six weeks, each patient was asked to rate his status, compared with that at the start of the trial, on a scale of "better," "worse" or "unchanged."

Data Analysis

In this study we used systematic alternating allocation of patients after initially randomly allocating in each severity category. Because masking prevented timing of patient enrollment from being influenced by anticipated patient assignment, we assume that patient arrival sequence was effectively random. Thus, for analysis purposes, we assume that the patient-allocation process was equivalent to that of a traditional randomized block design.

Significance tests are used to check whether the outcomes of the two treatments differ more than could be expected from chance alone. Confidence intervals are used to aid judgments about the clinical equivalence of the two treatments.

Comparability of the baseline characteristics of the two treatment groups was assessed by χ^2 or t test for categorical or continuous characteristics, respectively. Differences in ointment use in the two groups were assessed by the randomized blocks version of the Wilcoxon rank sum test,[10] because mean ointment use differed considerably in different severity categories. Differences in therapeutic response were tested by the standard Wilcoxon rank sum test, because there was little relationship between severity and therapeutic response. Similarly, approximate confidence intervals for the difference in mean therapeutic responses based on the t distribution were constructed without considering blocking, and consequently may be somewhat larger than necessary.

Results

Demography and Clinical History

Of the 52 patients who completed the study, 48 were white, 2 were black and 2 were Filipino. All were male.

Table 2 shows that patients in the traditional-dose and the reduced-dose groups did not differ significantly

TABLE 2.—*Baseline Comparison of Patients by Treatment Group*

Characteristic	Traditional-Dose Group (n=27) Mean	SD	Reduced-Dose Group (n=25) Mean	SD	P*
Age (years)	58.78	10.29	57.68	15.31	.76
Age at onset of disease (years)	32.74	14.37	32.68	14.51	.98
Therapy Immediately Before Entering Study (% of patients)					
	(%)		(%)		
Topical steroids and topical tars	33.3		32.0		.12
Topical steroids only	40.7		64.0		
Topical tars only	11.2		0.0		
Neither	14.8		4.0		

*t Test for continuous characteristics; χ^2 test for the categorical characteristic.

with respect to current age, age at onset of psoriasis or prior treatment for psoriasis.

Use of Fluocinonide

Table 3 shows the average amount of fluocinonide used by the patients in each severity category in each treatment group. Overall, the traditional-dose group used 3.25 times more fluocinonide than did the reduced-dose group. However, when the average amount of vehicle used per patient in the reduced-dose group (230 grams) is added to the average amount of fluocinonide used (132 grams), there is no significant difference between the two groups in the average total amount of ointment applied (two-sided $P=.28$).

Patient Therapeutic Response

Table 4 shows that there was no significant difference in the distributions of therapeutic responses in the two treatment groups, as judged by the dermatologists. The mean therapeutic response of each group shows improvement after two weeks and after six weeks. Most of the therapeutic gain was achieved during the first two weeks. The therapeutic response of the reduced-dose group was consistently judged better than that of the traditional-dose group. Moreover, the upper limits of the 95% confidence intervals for the difference in mean response provide good evidence that the traditional dose was not clinically superior to the reduced dose in these patient groups. No adverse side effects were observed in either group.

Based on patients' self-evaluations, shown in Table 5, practically all patients in the traditional-dose group and the reduced-dose group believed their treatment had improved their psoriasis both after two weeks and after six weeks. Although each dermatologist also rated most patients as showing improvement, they judged more patients as showing no change than did the patients themselves. The few patients who said they were worse or were judged worse by the dermatologists were fairly evenly divided between the traditional-dose group and the reduced-dose group.

Discussion

For this patient population there is good evidence that the traditional-dose regimen is not clinically superior to the reduced-dose regimen. Thus the results

TABLE 3.—*Mean Amount (in Grams) of Fluocinonide Used per Patient During Trial*

Treatment Group	Category: Mild	Moderate	Severe	Total
Traditional dose	270 (n=17)	538 (n=9)	2,160 (n=1)	429 (n=27)
Reduced dose	76 (n=17)	206 (n=7)	570 (n=1)	132 (n=25)
Ratio $\frac{\text{Traditional dose}}{\text{Reduced dose}}$ ..	3.55	2.61	3.79	3.25

TABLE 4—*Dermatologists' Evaluations of Therapeutic Response on a Seven-Point Scale Based on Photographs Taken at Two and Six Weeks From Baseline*

Evaluation Time	MD*	Treatment Group†	Percent at Each Response Score‡ −3	−2	−1	0	+1	+2	+3	P§	Mean Score	95% Confidence Interval for the Difference in Mean Scores (TD—RD)
Two Weeks												
	#1	TD	0.0	0.0	0.0	25.9	59.3	14.8	0.0	.066	.89	(−0.73, 0.029)
		RD	0.0	0.0	0.0	16.0	44.0	40.0	0.0		1.24	
	#2	TD	0.0	0.0	7.4	37.0	25.9	29.6	0.0	.032	.78	(−1.26, −0.12)
		RD	0.0	0.0	0.0	24.0	28.0	24.0	24.0		1.48	
	#3	TD	0.0	0.0	0.0	14.8	48.2	29.6	7.4	.083	1.30	(−0.89, 0.036)
		RD	0.0	0.0	0.0	4.0	40.0	36.0	20.0		1.72	
Six Weeks												
	#1	TD	0.0	0.0	3.7	22.2	59.3	14.8	0.0	.099	.85	(−0.79, 0.094)
		RD	0.0	0.0	4.0	12.2	48.0	32.0	4.0		1.20	
	#2	TD	0.0	0.0	3.7	29.6	40.7	14.8	11.1	.072	1.00	(−1.20, 0.16)
		RD	0.0	4.0	4.0	16.0	16.0	32.0	28.0		1.52	
	#3	TD	0.0	0.0	0.0	11.2	33.3	33.3	22.2	.475	1.67	(−0.72, 0.46)
		RD	0.0	0.0	4.0	12.0	16.0	36.0	32.0		1.80	

*MD #1 was the Principal Investigator who also examined the patients weekly during follow-up.
†There were 27 subjects in the traditional-dose (TD) group and 25 subjects in the reduced-dose (RD) group.
‡See Table 1 for explanation of 7-point scale.
§Two-sided statistical significance of group difference by the Wilcoxon rank sum test.

TABLE 5.—*Patient Self-Evaluation at Two and Six Weeks From Baseline*

Time	Treatment Group	Percentage of Patients: Worse −1	No Change 0	Better +1	Mean	P*
Two Weeks	Traditional dose	0.0	7.4	92.6	.93	.57
	Reduced dose	0.0	12.0	88.0	.88	
Six Weeks	Traditional dose	7.4	3.7	88.9	.81	.69
	Reduced dose	4.0	4.0	92.0	.88	

*Two-sided statistical significance of group difference by Mann-Whitney rank sum test.

of this clinical trial support the more general hypothesis that in adult male outpatients with stable psoriasis, there is no clinically important difference between the therapeutic response of four-times-a-day applications of fluocinonide and applications at bedtime of fluocinonide combined with three-times-a-day applications of its vehicle. This conclusion differs somewhat from that of another study[4] that found a greater percentage of patients had good results from multiple applications of a fluorinated topical steroid, 0.1% halcinonide cream, than did patients who had single applications. Because the methods used in the other study differed considerably from those used in the study reported here and because certain details about their methods were not reported, the reasons for the different findings are difficult to explain. Several studies have reported, however, that the use of corticosteroids in an ointment base results in more biologic activity and percutaneous penetration—and the subsequent achievement of greater clinical efficiency—than does the use of the same therapeutic agent in a cream base.[2,11,12]

If subsequent studies show that application of fluocinonide at bedtime without application of its vehicle is as effective as application of fluocinonide four times a day, or if an inexpensive skin moistener or emollient is as effective as the vehicle, then significant cost saving is possible. In a survey of 11 pharmacies in the San Francisco Bay Area it was found that the price of a 60-gram tube of Lidex ranged from $17.45 to $24.95. The annual costs reported here are based on the median price of $19.16 per 60-gram tube and on the amounts used by patients with mild and moderate psoriasis reported in Table 3. Based on these data, a person with mild psoriasis applying fluocinonide each night would spend $210 per year instead of $747 for four-times-a-day applications, a saving of $537. For persons with moderate psoriasis, the expenditure would be $570 per year instead of $1,489, a saving of $919.

If applications of fluocinonide at bedtime only are as effective as applications four times a day, the reduction in the frequency of applications may improve patient compliance with the drug regimen. Although little appears in the literature about studies of the correlation between frequency of application of topical medications and compliance, it is difficult to believe that it would differ from what is known about frequency of dosage and compliance with medicine taken by mouth. Several studies suggest that compliance decreases as frequency of dosing increases.[13-15]

The finding of this study has implications for the long-term management of psoriasis. Although topical application of corticoids is effective, significant and potentially serious adverse side effects are well-known sequelae of this therapy.[16-18] These adverse side effects include both local and systemic effects. Local adverse effects include acne, telangiectasia, hypertrichosis, hypopigmentation, striae, miliaria and atrophy. Significant systemic effects include the suppression of the pituitary-adrenal axis and all the consequences of Cushing's syndrome.[2,19] Clearly, any therapeutic maneuvers that might reduce the frequency of both local and systemic adverse effects by reducing the amount of topical steroids used in treatment would be worthwhile.

Tachyphylaxis to multiple applications a day of topical corticoids is another adverse effect that might occur less often with less frequent applications. Topical corticoids may exert their therapeutic activity in psoriasis by inhibiting epidermal DNA synthesis and mitosis.[20] Du Vivier and co-workers have shown that tachyphylaxis to the inhibition of epidermal DNA synthesis developed rapidly in hairless mice.[21] Although their work showed this effect to persist for as long as 192 hours, any change in topical therapy designed to lengthen the interval between applications of topical corticoids might help to reduce the impact of this troublesome phenomenon.

Before one can state that once-a-day application of fluocinonide is as effective in the treatment of chronic psoriasis as four-times-a-day application, further study is needed to determine whether the drug vehicle used in this study had any therapeutic effect. Further investigation is also required to determine whether our findings also apply to other types of steroid-responsive dermatosis such as eczema or seborrhea. Nevertheless, the results of this trial point to the importance of studies designed to validate treatment regimens.

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Prolactin-Secreting Pituitary Adenomas

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Prolactin-secreting pituitary adenoma is a common cause of gynecologic problems that include oligomenorrhea, infertility, amenorrhea and galactorrhea. Diagnosis requires a combination of endocrine testing and radiologic evaluation. The diagnosis of macroadenomas is usually straightforward and these large tumors may be associated with mass effects such as severe headache, nerve palsies or visual changes. Microadenomas may be more subtle in presentation, and the diagnosis of hyperprolactinemia without radiologic evidence of a tumor frequently is problematic. The management of prolactin-secreting adenoma remains controversial, with no clear consensus or indication for surgical versus medical treatment. Surgical intervention is a realistic option for those patients who have access to an experienced neurosurgeon and who have tumor characteristics that offer a reasonable hope for cure. Many questions remain to be answered, including the cause, natural history of development and the optimum treatment for individual cases.

The ability to quantify prolactin in serum and other body tissues by means of highly specific and sensitive assays, coupled with advances in neuroradiologic techniques, has led to the ability to diagnose a surprisingly common clinical disorder: prolactin-secreting adenomas, often associated with amenorrhea and galactorrhea. It remains to be ascertained whether the increased frequency with which these tumors are diagnosed is due to improved ability to detect them radiologically, the capacity to quantify circulating prolactin or all of these plus a new etiologic factor or factors.

Radiologic Detection

In the past, standard anteroposterior and lateral x-ray films of the sella turcica were used to determine whether a pituitary neoplasm existed in patients who had galactorrhea and amenorrhea. Subsequently, it was found that hypocycloidal sellar polytomography could be used to detect subtle changes in the sella that often were not evident using plain films.[1] Indeed, in one study[2] we found that more than half of a group of plain films of the sella were interpreted as normal, though sellar polytomography indicated the presence of a pituitary adenoma, subsequently confirmed at operation. Therefore, polytomograms with 1- or 2-mm interval sections were recommended, rather than plain films of the sella, when a pituitary adenoma was suspected. Recently, high-resolution computed tomography (CT scanning) has proved valuable in detecting adenomas and has become the procedure of choice for diagnosing a pituitary adenoma (Figure 1). Presently available instrumentation allows definitive resolution of most tumors as small as 7 to 10 mm in size.[3] The radiation involved is about 3 to 5 rads to the lens. The use of CT scanning has obviated the need for pneumoencephalography to ascertain the extent of enlargement of pituitary tumors and has permitted the direct diagnosis of the empty sella syndrome, a condition in which the dura herniates into the sella, with associated sellar enlargement. The injection of metrizamide dye either intravenously or, in some cases, intrathecally is a further aid to differentiation of this syndrome, and it visually enhances adenomatous tissue when present.[4,5]

Prolactin-secreting tumors are usually found in the lateral aspects of the pituitary, often with anteroinferior expansion of the sellar floor accompanied by cortical bone thinning. As lactotropes are found primarily in a lateral location in the normal pituitary, it is not surprising that this is the most frequent site of tumor formation. In one study[6] we found that in all pituitary abnormalities that led to transsphenoidal surgical exploration in which no tumor was encountered, tomographic findings suggested that a central pituitary lesion was present. Therefore, extreme caution should be

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ABBREVIATIONS USED IN TEXT

CT=computed tomography
FDA=Food and Drug Administration

exercised before making the diagnosis of a midline prolactin-secreting tumor.

The recent development of nuclear magnetic resonance (NMR) as a tool for radiologic diagnosis offers hope that this technology will replace the use of ionizing radiation and permit the diagnosis of these types of tumors with the same or improved degrees of resolution with added safety.

At present the choice of radiologic evaluation technique is determined by cost and availability. Currently we recommend that high-resolution CT scanning be considered the procedure of choice.

Detection by Hormone Assay

For clinical purposes, radioimmunoassay is currently the most common method for quantifying prolactin. The upper limits of normal in most laboratories are between 15 and 20 ng per ml. Any persistent elevation of prolactin is reason for investigation, and adenomas have been found associated with prolactin concentrations as low as 23 ng per ml. It is our opinion that a prolactin measurement should be done in any nonpregnant woman who has breast secretions, whether spontaneous or expressible and whether or not there is associated amenorrhea. In addition, in all patients with unexplained amenorrhea the serum prolactin level should be measured, regardless of whether there is accompanying galactorrhea, because hyperprolactinemia has been found in about 15% of patients who have unexplained amenorrhea unaccompanied by galactorrhea. Patients with oligomenorrhea and infertility patients with evidence of a short luteal phase or with unexplained infertility also should be tested for hyperprolactinemia.

Increases in circulating prolactin concentration can occur in a variety of circumstances (Table 1). These include use of certain medicines, trauma to the chest wall and excessive nipple stimulation, as well as abnormalities of the pituitary gland. Medications that can increase prolactin concentrations include dopamine antagonists (receptor-blocking agents) such as phenothiazines, butyrophenones, metoclopramide, sulpiride and pimozide; catechol-depleting agents such as reserpine and methyldopa, and dopamine reuptake blockers such as imipramine and amphetamines. In addition, estrogen-containing drugs, including oral contraceptive agents, may raise circulating prolactin levels. Other conditions also are associated with elevations in prolactin. Scarring from a surgical procedure, other forms of trauma to the chest wall or herpes zoster may cause persistent hyperprolactinemia. An abrupt increase in prolactin has been found within 45 minutes of food ingestion.[8] Physical or emotional stress can trigger a significant prolactin increase. There are also physiologic increases associated with sleep, a slight increase associated with the luteal phase shown in a few studies[9] and increases that occur early in pregnancy coincident with the rise in estrogen levels.[10] Opiates will increase prolactin, and acute administration of cimetidine, a histamine antagonist, will induce a transient increase in prolactin. This effect disappears with long-term administration.[11]

Provocative Testing

Because so many factors can lead to an isolated raised prolactin value, the diagnosis of hyperprolactinemia requires demonstration of persistent elevation. This can be accomplished by repeated sampling, over days or hours, to minimize both laboratory variations and random elevations. We use this opportunity to rule out abnormalities of thyroid-stimulating hormone, growth hormone and pituitary-adrenal function, at the same time confirming the abnormality in prolactin secretions by doing a thyrotropin-releasing hormone provocative test or an insulin tolerance test, or both. This usually also serves as a preoperative functional screen for patients who subsequently will undergo transsphenoidal resection, and provides a baseline for future follow-up.

Several provocative tests have been proposed in attempts to discriminate between tumorous and nontumorous hyperprolactinemia. These include the use of thyrotropin-releasing hormone, insulin-induced hypoglycemia, levodopa, chlorpromazine, domperidone,

Figure 1.—High-resolution computed tomogram showing pituitary adenoma with suprasellar extension.

nomifensine and benserazide.[12-18] To date, no test has proved universally reliable in detecting the presence of an adenoma, and a combination of persistently elevated prolactin levels with radiologic evidence of an adenoma is still required for diagnosis.

Classification

Adenomas are classified by size, location, behavior and hormone production. Microadenomas are defined as smaller than 10 mm and macroadenomas are tumors larger than 10 mm. This classification may be based on surgical specimen measurements or on radiologic assessment.

An anatomic (radiologic and operative) classification of pituitary adenomas, a modification of Hardy's classification scheme,[19] has been used at our institution.[20] Briefly, grade I tumors are less than 10 mm in diameter and confined entirely within the sella; the sella may be focally expanded, but usually it is intact. Grade II tumors are larger than 10 mm and do not penetrate the sella floor; the sella is almost always enlarged. Grade III tumors focally perforate the dural membrane and cortical bone of the anterior wall and floor of the sella and extend into the sphenoid sinus or sphenoid bone. Grade IV tumors perforate these structures diffusely. Grade V tumors spread via the cerebrospinal fluid or hematogenous routes.

Stage 0 tumors have no suprasellar extension. Stage A tumors occupy the suprasellar cistern but do not deform the third ventricle. Stage B tumors occupy the suprasellar cistern and obliterate only the anterior recesses of the third ventricle. Stage C tumors obliterate the anterior recesses of the third ventricle and deform and elevate its floor. Stage D tumors have intradural, intracranial extension; subscript numbers 1, 2 and 3 designate extension into anterior, middle and posterior fossa, respectively. Stage E tumors invade the cavernous sinus through the lateral dural envelope of the sella.

It is rare to find metastasis from prolactin-secreting adenomas; in a recent case report from this institution, however, a malignant tumor with distant metastasis

TABLE 1.—*Causes of Increases or Decreases in Circulating Prolactin Concentration**

Physiologic Causes	*Pharmacologic Causes*	*Pathologic Causes*
Elevated Prolactin Concentration		
Sleep	TRF	Prolactin-secreting pituitary tumors (with or without galactorrhea)
Exercise	Estrogen therapy	Hypothalamic disorders: functional (for example, irradiation; pseudocyesis); organic (for example, primary or metastatic tumor)
Stress (such as surgical procedure)	Anesthesia	Hypothyroidism
Late follicular phase of cycle	Dopamine receptor blocking agents Phenothiazines Butyrophenones Metoclopramide Sulpiride Pimozide	Nelson's syndrome Acromegaly
Pregnancy	Catechol-depleting agents Reserpine α-Methyldopa (Aldomet)	Renal failure
Puerperium	Reuptake interference Imipramine hydrochloride Amphetamine	Ectopic production Bronchogenic carcinoma Hypernephroma
Suckling	Arginine infusion	Pituitary stalk section
Amniotic fluid	Insulin-induced hypoglycemia	
Fetus		
Newborn		
Response to electroshock therapy		
Decreased Prolactin Concentration		
During parturition	Dopamine receptor agonists Apomorphine Bromocriptine LSD Levodopa Dopamine	Anorexia nervosa
	MAO inhibitor Pargyline hydrochloride	Hypophysectomy (complete)
	Glucocorticoids and dexamethasone	

TRF = thyrotropin-releasing factor, MAO = monoamine oxidase.

*From Yen and Jaffe.[7]

was described.[21] The metastasis appeared late after unsuccessful attempts at transsphenoidal resection and radiation therapy.

Morphology of Prolactin-Secreting Pituitary Tumors

Grossly, pituitary adenomas usually originate in the lateral aspects of the anterior pituitary where mammotropes are most abundant. As they enlarge, a pseudocapsule forms around the tumors, which facilitates their removal.[22] These tumors usually are softer than the surrounding pituitary and may be discolored (gray, brown or blue) as a result of hemorrhage into the tumor. Although most are solid, they also may be cystic or show evidence of degeneration.

The parenchymal cells of the anterior pituitary are usually densely arranged in cords or small lobules such that individual cells are never more than one or two cells from contact with a pericapillary space or sinusoid. Lobules are surrounded by a basement membrane, and the pericapillary space contains a loose collagen network and occasional connective tissue elements. Most of the cells have the same basic structure, differing mainly in their size and shape and the size, shape and number of their secretory granules. Differences in the configuration of the rough endoplasmic reticulum and Golgi apparatus also have been noted.

In the first report dealing with the ultrastructure of the human anterior pituitary, there was no attempt to classify cell types.[22] Since then, several descriptive studies have been published using tissue obtained at autopsy or hypophysectomy.[23-25] Generally, there is good agreement among these reports regarding morphology and granule size for specific human cell types and good correlation with those in other species.

With the purification of pituitary hormones and the specificity afforded by antibodies against these hormones, the functional roles of adenohypophyseal cell types were explored further by various immunohistochemical techniques. Immunofluorescent methods involving light microscopy were used,[26-29] and immunoferritin was located by means of electron microscopy.[30] Immunoenzyme techniques, however, have been the most extensively used in studies of pituitary cytophysiology. There have been several excellent reviews of this subject.[31-35]

The control of synthesis and discharge of secretory granules is mediated by hypothalamic-releasing and inhibiting factors that are secreted into portal blood following appropriate stimulation. Pituitary hormone synthesis and secretion appear to be similar in all adenohypophyseal cell types.[36,37] The usual signs of active hormone synthesis include a well-developed rough endoplasmic reticulum and a hypertrophied Golgi region containing progranules that aggregate, forming secretory granules. Newly synthesized protein has been followed from rough endoplasmic reticular cisternae to the Golgi region by both immunohistochemistry and autoradiography.[30,36,38] In the Golgi region, progranules are transformed to immature granules, which fuse with one another to form granules of mature size that are dispersed throughout the cytoplasm or come to lie beneath the plasmalemma.

Granule discharge usually occurs by exocytosis[36,37,39,40] though exocytosis may not be the only means of pituitary hormone secretion. Pituitary adenomas continue to secrete hormones even in long-term cultures in the absence of hypophyseotropic factors without showing exocytotic profiles.[41] Pituitary tumors, therefore, including the so-called chromophobe adenomas, may secrete hormones in the absence of signs of mature granule formation and extrusion.

Immunoperoxidase techniques have confirmed that gonadotropic cell types are distributed throughout the human pars distalis but are concentrated posteromedially, being less numerous anterolaterally.[34,42] Lactotropes also appear in the posteromedial zone near the residual cleft, but they are found predominately in the lateral wings of the pars distalis. As indicated previously, this lateral location corresponds well to the reported sites of adenomas associated with galactorrhea and amenorrhea.

Although these tumors originally were considered to be chromophobic,[43] granules within the cells subsequently were shown to be erythrosinophilic,[44] a characteristic of prolactin-producing cells in normal glands.

Several reports of the ultrastructure of these adenomas have appeared.[45-47] The tumor mass consists of polygonal cells with a large round or oval nucleus. A few large, polymorphic secretory granules reach the normal 700 nm in diameter or larger, but smaller, rounded granules are often observed. Most granules measure 400 to 500 nm in diameter, which has been judged to be characteristic of adenomas producing this syndrome.[45] This small size may indicate the secretion of less-than-mature secretory granules due to the high rate of prolactin output. Fragments of this tumor in culture can secrete several hormones—such as growth hormone—indicating that these aberrant adenomas may produce proteins other than prolactin.

Incidence

Some clinicians have been concerned that the emphasis on early diagnosis and treatment of prolactin-secreting microadenomas is unnecessary and perhaps unwarranted because tumors may be very common, slow-growing and benign. This thesis is supported by a study by Costello,[48] who reported finding microadenomas in 22.5% of 1,000 cases autopsied, none of which had had symptoms of pituitary dysfunction. However, two lines of evidence suggest that not all of these were prolactin-secreting adenomas. First, the adenomas in Costello's study were found in persons as young as 2 years and as old as 86 years, with the greatest incidence in the sixth decade of life. In addition, 27% of the tumors were basophilic. Second, in a report by Trouillas and co-workers,[49] two types of adenomas were found in women with galactorrhea and amenorrhea: prolactin-secreting adenomas in a

group of young women (mean age, 26 years) and nonprolactin-secreting adenomas in a group of older women (mean age, 53 years). It appears, therefore, that information obtained from past studies regarding incidence or natural history of pituitary adenomas may not apply to prolactin-secreting adenomas occurring in young women who have amenorrhea or galactorrhea.

Keye and colleagues[50] attempted to ascertain the frequency of abnormal findings on tomograms, hyperprolactinemia and prolactin-secreting adenomas in women with amenorrhea or galactorrhea, or both. They also assessed the specificity of tomographic abnormalities in combination with hyperprolactinemia in the diagnosis of these tumors. Findings suggesting an adenoma were reported in about 25% of previously unscreened patients with amenorrhea or galactorrhea or both (that is, those who had not previously been evaluated for a prolactin-secreting pituitary tumor) and about 60% of prescreened patients (that is, those who had had a radiograph of the sella or a serum prolactin measurement before their referral).[50] The combination of an abnormal tomographic finding and elevated prolactin level was relatively specific for an adenoma.

Wolf and associates[51] reviewed the incidence of hyperprolactinemia in 500 anovulatory women, and found that 2 of 60 women with primary amenorrhea had hyperprolactinemia. Of 298 women with secondary amenorrhea, 23% had increased prolactin secretion, of whom 37% had radiologic evidence of tumors by sellar tomography. Finally, of 138 women with anovulatory oligomenorrhea, 19% had hyperprolactinemia. Only 50% of all of these women had galactorrhea.

Although galactorrhea is most commonly a symptom of hyperprolactinemia, it is important to recognize that not all patients with adenomas or hyperprolactinemia have galactorrhea, and not all women with galactorrhea have prolactin-secreting tumors. We have encountered prolactin-producing tumors in women with amenorrhea but no galactorrhea, with galactorrhea that was not present spontaneously but only on expression and with galactorrhea and regular menses. The absence of galactorrhea in the presence of hyperprolactinemia reflects that prolactin is necessary, but not sufficient, for the production of breast milk.

Clinical Features

Headache is the most commonly reported symptom, may be associated with all types of pituitary adenoma, may vary in intensity and location and may be nonspecific in character. Loss of visual acuity or visual field defects result from suprasellar extension and pressure on the inferior aspect of the optic chiasm; bitemporal hemianopsia is the classic ophthalmologic finding, but other visual defects may occur, depending on the location of the tumor and the direction of its growth. Large tumors with lateral extension and compression of the cavernous sinus may cause impairment of the third, fourth and sixth cranial nerves, resulting in extraocular nerve palsies, diplopia and visual loss. With the current emphasis on early diagnosis, it is uncommon to encounter neurologic symptoms or severe headaches in most patients with prolactin-secreting tumors, particularly with the more common microadenomas.

Rarely, a prolactin-secreting adenoma presents with the acute onset of severe headaches, rapid visual failure, extraocular muscle palsies and acute pituitary insufficiency with hypotension, rapid mental deterioration, coma and death. This constellation of events occurs as the result of "pituitary apoplexy" in which there is sudden expansion of the intersellar contents and subsequent interference with the blood supply to the pituitary. This leads to ischemia, necrosis and hemorrhage into the adenoma and the surrounding tissue.[52] Although these conditions may resolve spontaneously or may result in complete destruction of the tumor on occasion,[53] the administration of adrenal corticosteroids and emergency decompression of the intrasellar contents may be necessary.

Signs and symptoms of gigantism, acromegaly or hyperthyroidism may develop in women who have adenomas that secrete growth hormone or thyroid-stimulating hormone in addition to prolactin.

Other clinical features seen in patients with prolactin-secreting adenomas include alterations in secretion or function of the ovary or adrenal glands (or both). Mild elevations in prolactin may not always disrupt ovulation, but can be associated with luteal inadequacy.[54-57] The cause of the luteal inadequacy is unknown, but some in vitro studies show a direct inhibitory effect of prolactin on progesterone production in the ovary.[58] A return to a normal plasma prolactin level is likely to reestablish adequate luteal function. We were unable to confirm an inhibitory effect of prolactin on progesterone production in monkey luteal tissue (R. F. Laherty, MD; D. Rotten, MD; M. Yamamoto, MD, and co-workers, unpublished data, September 1981).

Pituitary adenomas have been described in some patients who have ovaries that appear polycystic.[59] The pathophysiologic relationship between hyperprolactinemia and polycystic ovarian disease is unknown; there is an increased incidence of elevated circulating androgens (particularly dehydroepiandrosterone sulfate).[60-62] Treatment of the hyperprolactinemia with bromocriptine[63,64] or surgical removal of the adenoma[65] results in return to normal of testosterone levels and of ovulatory menses in some of these patients with both disorders.

Diabetogenic properties have been attributed to prolactin. Prolactin-producing adenomas have been associated with metabolic abnormalities characterized by hyperlipidemia, low plasma lipoprotein lipase activity and insulin resistance.[66] After removal of adenomas, glucose tolerance was improved. However, tolerance was not improved after normalization of prolactin with bromocriptine.

A relationship between dopaminergic pathways, pro-

lactin and mental illness has been described. Women with hyperprolactinemic amenorrhea have been reported to have more symptoms of depression, hostility, emotional lability and anxiety than women with amenorrhea and normal concentrations of prolactin.[67] A recent, rapid and often excessive weight gain has been a presenting symptom of many hyperprolactinemic women. These symptoms tend to remit following treatment with bromocriptine or removal of an adenoma.

Patients who have primary hypothyroidism may mimic, in some respects, those who have prolactin-producing pituitary tumors.[68] It is likely that this is because primary hypothyroidism leads to elevation of hypothalamic thyrotropin-releasing hormone (TRH), which can stimulate prolactin as well as thyroid-stimulating hormone (TSH). Thus, these patients may have galactorrhea, hyperprolactinemia, amenorrhea and an enlarged sella turcica due to compensatory pituitary hypertrophy. In addition, they usually have signs and symptoms of hypothyroidism. The authors routinely get a measurement of thyroid-stimulating hormone when a pituitary tumor is suspected on the basis of raised prolactin levels and a radiologically enlarged sella turcica. Thyroid hormone replacement is the appropriate therapy for hypothyroidism.

Although much less commonly diagnosed than in women, increased prolactin concentrations may occur in men, in whom they may be associated with impotence. Mean testosterone concentrations in this group are significantly lower than the mean testosterone level in normal men.[69] Probably because they are seldom diagnosed early, tumors in men often are large and associated with extremely high prolactin levels, as well as with headaches and visual field impairment.

Cause

The process that causes or permits pituitary adenoma to develop has not yet been established. There are several hypotheses that have generated some experimental data, but the results have been inconclusive to date. Because pituitary adenomas remain responsive to the inhibitory effects of dopamine agonists, and because surgical removal results in a significant cure rate with a low incidence of recurrence, it has been proposed that these tumors develop in an environment of reduced dopamine concentration, reduced dopamine sensitivity or as a result of a vascular isolation that effectively prevents portal dopamine from perfusing the lactotropes involved. Portal dopamine concentration has not been measured in normal humans. However, that patients have normal prolactin levels immediately after excision of an adenoma suggests that there is sufficient portal dopamine to suppress the remaining normal pituitary lactotropes. The possibility remains that there may be a transient decrease in portal dopamine that would permit adenomatous tissue to develop and then return to normal levels, which then would be inadequate to control the hypersecretion of prolactin. The hypothesis concerning reduced dopamine sensitivity has been tested in a variety of experiments both in vivo and in vitro.[70-73] We were not able to show a loss of dopamine sensitivity in tumor tissue, examined in dispersed cell culture,[70] in tissue culture[70] or in vivo (M. C. Martin, MD; R. I. Weiner, MD; S. E. Monroe, MD, and colleagues, unpublished data, June 1982). Using low-dose dopamine (in the nanomolar range) there were no significant differences between the concentration of dopamine required to suppress 50% of prolactin in either normal control subjects or patients with adenomas. These results differ from those reported by other workers,[71] who used different criteria for sensitivity of the tumors and examined significantly higher amounts of dopamine. In these instances, findings were interpreted as showing a slight loss of sensitivity in the tumor groups relative to the normal controls. Finally, several investigators have suggested that adenomas may develop as a result of vascular sequestration, preventing portal circulation from perfusing the lactotropes, thus precluding dopaminergic inhibition and allowing hyperplasia and adenoma formation to occur.[72,73] This again may be a transient process in some cases. No experimental data have yet been generated to test this hypothesis.

Treatment

The objectives of therapy for prolactin-secreting tumors are (1) to prevent damage to normal pituitary tissue and the neurologic sequelae that accompany the progressive enlargement of these tumors, (2) to establish fertility in anovulatory women and (3) to eliminate lactation.

There is not universal agreement, however, that all of these tumors should be treated. Unlike growth hormone-secreting and adrenocorticotropic hormone-secreting tumors, usually there is no increased mortality or serious morbidity with chronically elevated prolactin levels. However, although the tumors are usually indolent, slow-growing and remain localized, microadenomas can be locally invasive, and we have had a patient with a metastatic, rapidly progressive tumor.[21] In addition, many of the patients have bothersome galactorrhea or involuntary anovulatory infertility and chronic estrogen deprivation. Because there is little information about the natural history of these tumors, it is not known how many microadenomas increase in size or the rate of growth of those that do enlarge. It may be reasonable to assume, however, that at least some of the large tumors began as microadenomas.

Forms of management that are available include drug therapy, surgical intervention, irradiation and close, periodic observation.

Drug Therapy

Formerly, the medical management of prolactin-secreting tumors was generally directed at the associated galactorrhea or amenorrhea, using exogenous sex steroids, clomiphene citrate or levodopa, usually with unsatisfactory results.

Bromocriptine mesylate (Parlodel), an ergot alkaloid and dopamine-receptor stimulator, is effective

TABLE 2.—*Frequency of the Most Common Adverse Reactions With Bromocriptine Mesylate Use**

Adverse Reactions	*US Clinical Trials Patients (N = 226) Dosage: 5-7.5 mg a day* Number (Percent)	*Published Studies† Patients (N = 737) Dosage: 2.5-10 mg a day‡* Number (Percent)
Nausea	115 (51)	192 (26)
Headache	41 (18)	50 (7)
Dizziness	37 (16)	29 (4)
Fatigue	18 (8)	4 (<1)
Abdominal cramps	15 (7)	4 (<1)
Hypotension/lightheadedness	13 (6)	49 (7)
Vomiting	12 (5)	17 (2)
Nasal congestion	11 (5)	4 (<1)
Constipation	7 (3)	34 (5)
Diarrhea	7 (3)	...
CNS: Insomnia	...	8 (1)
Depression		
Anxiety		
Anorexia		
Vertigo		
Dyspepsia	...	24 (3)

CNS = central nervous system.

*From Parlodel infertility monograph.[84]
†Excludes reports in which adverse reactions were not mentioned.
‡In some patients, the dosage reached 40 mg a day, but most received 2.5 to 10 mg a day. The maximum recommended dosage of bromocriptine therapy in the United States for female infertility is 7.5 mg a day.

in decreasing serum prolactin, causing the disappearance of galactorrhea and the return of menses in most women with prolactin-secreting pituitary adenomas.[74-78] There have been several reports of arrested growth or regression of tumor size during the administration of bromocriptine.[79-82] Mixed tumors, those producing growth hormone and prolactin, are more resistant to bromocriptine suppression and may require higher doses to achieve a decrease in size and normalization of hormone values. Isolated reports of tumor growth during or immediately after bromocriptine therapy are cause for concern, and suppression of prolactin may not be sufficient reassurance of successful tumor regression.[83] A follow-up CT scan therefore is recommended.

The major advantage of medical therapy is its efficacy, with a low rate of side effects after initial tolerance is established (Table 2). The major disadvantages are failure to achieve a permanent cure—requiring long-term maintenance therapy—and in a few patients, an intolerance to side effects. Among these complaints are nausea, dizziness and gastrointestinal upset.

Because of the suppression of tumor size achieved with bromocriptine, it is presently being evaluated as a method of preoperative treatment in patients with suprasellar tumors, in the hope of improving surgical cure rates. Initial reports suggest that preoperative treatment of microadenomas with bromocriptine may not be helpful[85] but may cause alterations of normal pituitary morphology, which create technical difficulties in distinguishing normal tissue from adenomatous tissue, thereby decreasing cure rates.

The major controversy surrounding the use of bromocriptine involves its use in the treatment of anovulatory infertility. Although it may be successful in inducing ovulation, in a small proportion of women with untreated tumors who become pregnant rapid tumor growth may occur, with temporary or permanent loss of vision.[86-90] At present, bromocriptine is not approved by the Food and Drug Administration (FDA) during the cycle of conception in patients with suspected tumors. Nevertheless, several investigators have used this form of therapy and it is probable that bromocriptine therapy has become the dominant mode of treatment for these tumors. The management of patients with adenomas who achieve pregnancy is discussed later.

Surgical Therapy

Transsphenoidal exploration of the sella with the radiofluoroscope and the operating microscope is used by several neurosurgeons for the selected removal of prolactin-secreting pituitary adenomas.[19,20] This approach has been useful for removing almost all pituitary adenomas, except in certain cases in which there is extensive suprasellar or lateral extension of the tumor. It is ideally suited for the selective removal of intrasellar adenomas, larger tumors with extension into the sphenoid sinus and tumors with minimal suprasellar extension. The expertise of the neurosurgeon is a critical factor in determining the morbidity and results obtained.

The selective removal of these tumors often is followed by a return of prolactin levels to normal and the cessation of galactorrhea and is accompanied by few complications when done by a competent, experienced neurosurgeon. We studied 46 women with prolactin-secreting pituitary adenomas and amenorrhea or galactorrhea (or both) to determine the influence of the selective transsphenoidal removal of these tumors on pituitary and reproductive function.[91] This procedure was effective in restoring menstrual function in 34 of 41 women and in eliminating lactation in 30 of 40 women. Tumor size and preoperative serum prolactin concentrations were the most important factors in predicting the postoperative disappearance of symptoms. Normal menstrual function returned in 33 of 34 women with tumors less than 2 cm in diameter but in only one of seven women with tumors larger than 2 cm. Similarly, galactorrhea ceased in 29 of 34 women with tumors smaller than 2 cm but in only one of six women with larger tumors. Among women who had preoperative serum prolactin levels below 200 ng per ml, menses returned in 31 of 32 patients and galactorrhea disappeared in 25 of 31; conversely, menses returned in only three of nine women and lactation ceased in one of six women with preoperative serum prolactin concentrations above 200 ng per ml. Prolactin concentrations decreased in 42 of 43 patients following the removal of a pituitary adenoma and returned to normal in 30. Postoperative pituitary reserves of adrenocorticotropic, growth, luteinizing and follicle-stimulating hormones were normal in most patients.

Thorner and co-workers[92] reviewed data from eight

different centers, and a wide range of results was reported. Results reported by Hardy and associates[93] represent the largest series and confirmed a difference between microadenomas—with a 90% surgical cure rate—and macroadenomas—with 40% to 50% cure rates. A recent review of 100 patients treated at the University of California, San Francisco (UCSF), showed 72% cure of grade I tumors and a 50% cure rate for tumors of larger size.[94] These studies indicate that the removal of prolactin-secreting pituitary adenomas by a neurosurgeon accomplished in this surgical technique is effective in restoring menstrual function and eliminating lactation in most women, especially if the tumor is less than 2 cm in diameter and the serum prolactin concentration is less than 200 ng per ml. Thus, the selective removal of these tumors appears to be effective in the treatment of the amenorrhea and galactorrhea with which these patients present. Postsurgical recurrence raises the question of whether this is the result of failure to remove the tumor in its entirety or is a new growth of a second adenoma. In most cases, especially with macroadenomas, incomplete resection can be documented and persistent hyperprolactinemia ascribed to relapse rather than a second tumor. The determination of whether there will be recurrent adenoma formation awaits further study.

Observation

Because many of the microadenomas are slow growing, and perhaps there is a significant group in which there is no growth, several investigators have recommended observation with periodic monitoring of prolactin concentrations and radiologic findings. However, an earlier report[95] and observations by our group[96] suggest that the amenorrhea and the hypoestrogenic state associated with hyperprolactinemia can lead to a decrease in bone density. We therefore feel that restoration of menses with consequent rise in estrogen level is advisable. Also, growth of tumor without significant increase in prolactin was reported in one study, making reliance on serum prolactin concentration inadvisable as the sole index of tumor size and suggesting repeated radiologic evaluation.[97] Until nuclear magnetic resonance techniques are widely available, even the low radiation dosages involved in CT scans may cause lens damage if studies are repeated frequently.

Radiation Therapy

Supervoltage irradiation for pituitary tumors consists of cobalt-beam irradiation with a dose of about 45 rads over a four- to five-week period.[98] This form of therapy may arrest the progressive enlargement of the tumor and may be followed by the cessation of lactation, but menses often do not return.[98] Although serious complications are rare, radiation therapy may be followed by various degrees of hypopituitarism,[99] perhaps due to hypothalamic damage, and serious sequelae, including cerebral radiation damage and death, have been reported.[100]

Proton-beam or heavy particle irradiation, available at a few centers, has been used most often in the treatment of growth hormone-secreting tumors. The effect is more rapid than with conventional irradiation, but it is not suited to treatment of tumors with pronounced extrasellar extension. Some centers advocate interstitial irradiation using surgically implanted isotopes such as yttrium. All of these forms of treatment are complicated by the possibility of late onset of hypopituitarism. The major benefit to be expected from radiation treatment is prevention of further growth of the tumor, but the severity of complications and the frequency of failure to normalize prolactin make it necessary to critically review indications for this type of therapy when medical management is an available option.

Management of Adenomas in Pregnancy

The ability to induce ovulation and pregnancy with bromocriptine has caused considerable controversy concerning treatment of women with adenomas who wish to become pregnant. A normal pituitary gland increases in size during pregnancy due to hyperplasia of prolactin-secreting cells probably resulting from increased estrogen stimulation. Rapid enlargement of an adenoma during pregnancy can result in headaches and visual disturbances.

In two reviews, a high incidence of complications during pregnancy was reported, primarily with macroadenomas. In women with unspecified tumor size,[101,102] 24% required surgical or radiation therapy either during or soon after pregnancy. When women were differentiated based on tumor size,[101] 95% of those with microadenomas had uneventful pregnancies and, of those with macroadenomas, 64% had complications, 37% requiring definitive treatment. In previously treated women, ony 1% to 2% required therapy. Although both of these studies are biased in favor of reporting complications, they document that complications can occur with all sizes of adenomas but the incidence is greatly increased with macroadenomas. In four recent reviews[103-106] involving 164 pregnancies in women who had microadenomas and macroadenomas, there was a remarkably low incidence of complications. Only one patient required treatment, which was postponed to the postpartum period. Bromocriptine has been used during pregnancy, though not yet FDA approved, to prevent complications with macroadenomas[107] and to cause rapid regression of suprasellar extensions of prolactinomas.[108]

There are no accurate ways of predicting tumor complications during pregnancy. Women with small adenomas may be given the option of medical versus surgical treatment before pregnancy but must be informed of the risks involved. Women with rapidly growing tumors or macroadenomas should have transsphenoidal removal of their tumor before pregnancy, or consider maintenance of bromocriptine throughout pregnancy. This treatment is not approved by the FDA, but has been reported in medical journals of both Europe and the United States.

Pregnancies in women with adenomas are managed

expectantly with monthly visual field examinations and serum prolactin determinations to detect rapid elevation. Treatment of complications is best accomplished with bromocriptine or surgical removal.

Summary

In the relatively few years since the isolation of prolactin and subsequent development of a specific radioimmunoassay, a great deal of information has been acquired regarding prolactin-secreting adenomas. Many questions remain to be answered, including their cause, the natural history of their development and the precise nature of the interaction between prolactin and the hypothalamus, gonad and adrenal glands. Until these fundamental problems are resolved, it will be difficult to deal unequivocally with the more clinically pressing dilemmas of who should be treated, when and with what modality. Judging from the rate of acquisition of recent information and the aggressive pursuit of solutions to these problems, more definitive statements should be forthcoming in the not-too-distant future.

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Specialty Conference

From Cyanotic Infant to Acyanotic Adult—The Odyssey of Blue Babies

Moderator
JOSEPH K. PERLOFF, MD

Discussants
WILLIAM F. FRIEDMAN, MD; HILLEL LAKS, MD, *and* JOHN S. CHILD, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. Director of Conferences: William M. Pardridge, MD, Associate Professor of Medicine.

In the past two decades we have witnessed the maturing of diagnostic and surgical skills in the management of congenital heart disease. Although longevity and quality of life have improved, cures are few; varying degrees of postoperative medical supervision are therefore needed. This new patient population of adults requiring long-term medical care continues to increase. Proper management of such patients can be taxing, requiring knowledge not only of the preoperative disease but also of the nature and effects of surgical intervention and of the presence, type and extent of late postoperative residua and sequelae. The tetralogy of Fallot is taken as a model because it is well known in both pediatric and adult medicine, because intracardiac repair includes a wide range of techniques and because postoperative residua and sequelae comprise a broad spectrum of patient care concerns.

JOSEPH K. PERLOFF, MD:* *In 1939 Dr John Hubbard, a Boston pediatrician, diagnosed patent ductus arteriosus in a child and Dr Robert Gross, a pediatric surgeon, ligated the duct. Dr Helen Taussig conceived the idea of creating a "patent ductus" in cyanotic children suffering from deficient pulmonary blood flow. Five years later in Baltimore, she made the diagnosis of tetralogy of Fallot, and Dr Alfred Blalock, an experienced vascular surgeon, turned down a subclavian artery and sutured its end to the side of the pulmonary artery, establishing the Blalock-Taussig anastomosis. (Dr William P. Longmire, Emeritus Professor and Chairman, Department of Surgery, UCLA School of Medicine, was Dr Blalock's first assistant at this historic operation.) Thus began a therapeutic era that brought together cardiologists and cardiac surgeons in what proved to be one of the most successful rehabilitation programs that medicine has witnessed.*[1] *Two new disciplines were created, pediatric cardiology and cardiovascular surgery, which have long since come of age. Although we can reflect on the past with considerable satisfaction, we are now obliged to look ahead and redefine our goals.*

Immense technical resources of contemporary medi-

*Professor of Medicine and Pediatrics, Division of Cardiology, Departments of Medicine and Pediatrics.

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cine are at our disposal, permitting remarkably precise anatomic and physiologic cardiac diagnoses and astonishing surgical feats. Survival patterns have been affected, often profoundly. What do we seek to accomplish with these formidable capabilities? The answer is clear: not merely long-term survival, but improved quality of life. Cardiac surgical intervention remains the most dramatic and useful therapy for patients with congenital heart disease. Complete cures are few, however, and postoperative medical supervision almost always remains important if not obligatory. Proper care of adults with postoperative congenital heart disease requires knowledge not only of the nature and effects of the surgical intervention, but also of the presence, type and extent of postoperative residua and sequelae. The ideal total correction (complete cure) is rarely achieved, and it is confined to two conditions: division of an uncomplicated, nonpulmonary-hypertensive patent ductus arteriosus and perhaps, but not necessarily, closure of an uncomplicated ostium secundum atrial septal defect in childhood. All other surgical repairs provide palliation, albeit sophisticated palliation. These operations leave behind certain obligatory abnormalities, some trivial, others serious, while they prolong life and improve its quality.

This conference focuses on the tetralogy of Fallot as a means of illustrating and discussing preoperative problems, surgical management and late postoperative benefits, residua and sequelae. The selection was made for several reasons. First, natural survival ranges from infancy to or beyond middle age, making the tetralogy the most frequent cyanotic malformation seen in adults. Second, surgical intervention in Fallot's tetralogy is the earliest "blue baby" operation, and the original operation is still commonly done. Third, the complexity of intracardiac repair requires a wide range of techniques as the anomaly varies from acyanotic to pulmonary atresia. Fourth, the postoperative benefits are gratifying, but residua and sequelae of operation encompass a broad variety of concerns.

Dr William F. Friedman will discuss the preoperative problem from its inception at birth or in early infancy. Dr Hillel Laks will report on palliative (shunt) operations and intracardiac repair. Dr John S. Child will focus on the benefits of a surgical procedure, the complications of shunts and the residua and sequelae of intracardiac repair.

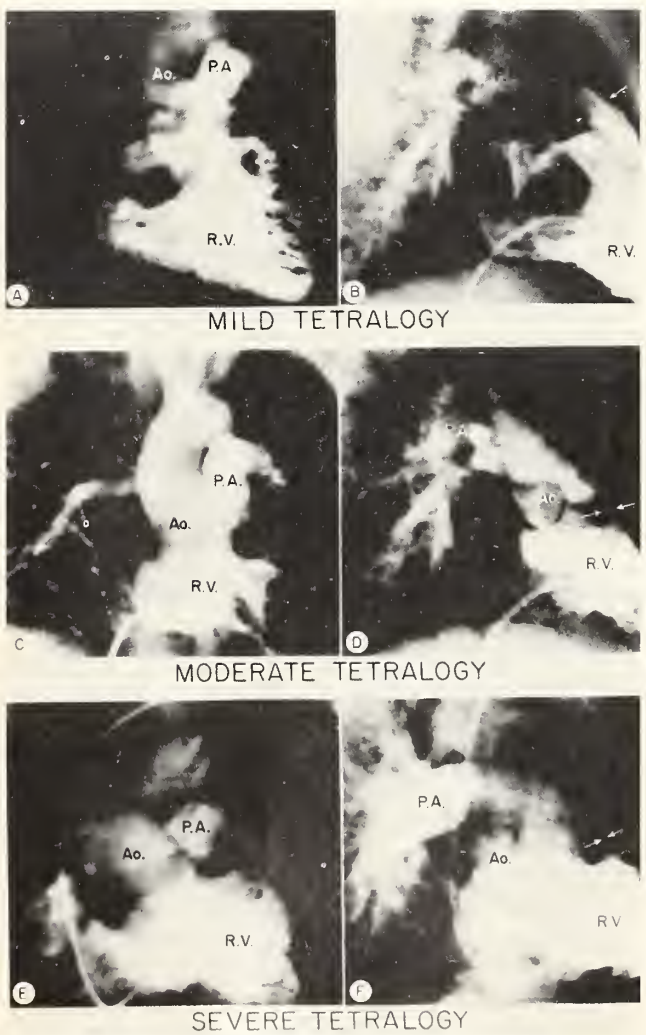

Figure 1.—Frontal **(left panels)** and lateral **(right panels)** views of right ventriculograms in children with tetralogy of Fallot, showing simultaneous opacification of the pulmonary artery (PA) and aorta (Ao). In the lateral frames, the arrows indicate the site and severity of infundibular obstruction. RV = right ventricle

The Preoperative Problem From Its Inception in Infancy

WILLIAM F. FRIEDMAN, MD:* The four anatomic components of the tetralogy of Fallot are ventricular septal defect, obstruction to right ventricular outflow, aortic override (straddle) of the ventricular septal defect and right ventricular hypertrophy. The basic anomaly is believed to result from an anterior deviation of the infundibular ventricular septum away from its usual location in the heart between the limbs of the trabecular septum. The ventricular defect is typically large and located just below the right cusp of the aortic valve separated from the pulmonic valve by the crista supraventricularis.[2,3] The aortic root may be displaced anteriorly, overriding the septal defect but, as in a normal heart, lying to the right of the pulmonary artery. In most cases, the overriding of the aorta is due to the subaortic location of the ventricular septal defect.

The severity of obstruction to right ventricular outflow is the principal determinant of the clinical presentation. The degree of hypoplasia of the outflow tract of the right ventricle varies from mild to complete (pulmonary atresia) (Figures 1 and 2). The infundibulum always becomes narrower. Pulmonary valve stenosis and supravalvar and peripheral pulmonary arterial obstruction may coexist, and unilateral absence of a pulmonary artery (usually the left) occurs in a few patients. Circulation to the abnormal lung is by systemic arterial collaterals.[4-7] Atresia of the pulmonic

*J. H. Nicholson Professor of Pediatric Cardiology and Chairman, Department of Pediatrics.

valve, infundibulum or main pulmonary artery is occasionally referred to as "pseudotruncus arteriosus." True truncus arteriosus with absent pulmonary arteries (type 4) differs from Fallot's tetralogy in which pulmonary artery branches are present but are perfused by systemic arterial collaterals or a patent ductus arteriosus (Figures 3 and 4[8]). A right-sided aortic arch and descending aorta occur in about 25% of patients who have tetralogy of Fallot. The coronary arteries may have variations that are surgically important.[9] The anterior descending artery sometimes originates from the right coronary artery, which may also give rise to a left branch coursing anterior to the infundibulum; a single left coronary artery may give rise to a branch that crosses the outflow tract of the right ventricle. Associated cardiac anomalies occur in about 40% of patients[10]; associated noncardiac anomalies are present in 20% to 30% of patients.[11]

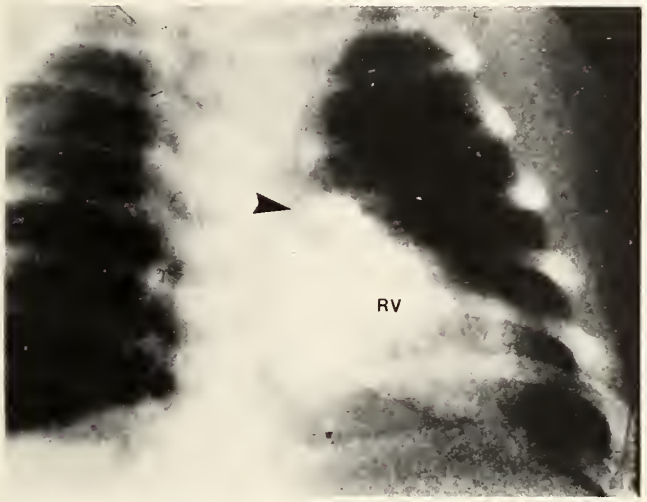

Figure 2.—A frontal view of a right ventriculogram in a 2-day-old infant with tetralogy of Fallot and pulmonary atresia. The right ventricular outflow tract **(arrow)** ends blindly. RV = right ventricle

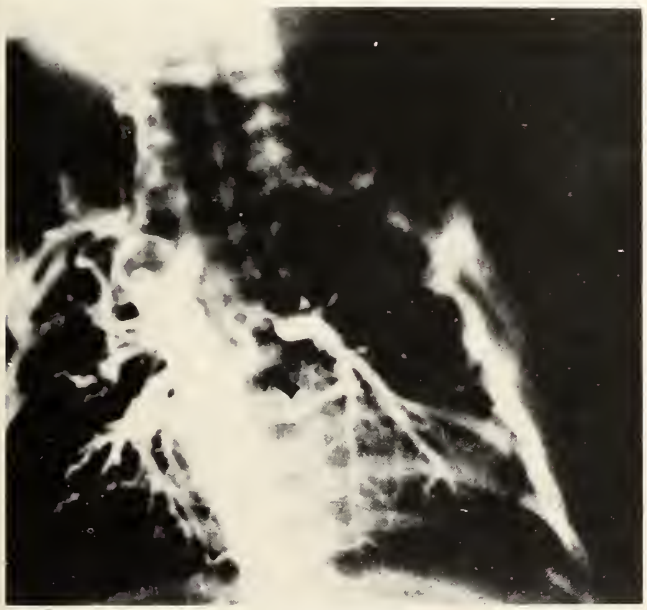

Figure 3.—A descending thoracic aortogram shows abundant systemic collateral arteries providing pulmonary blood flow in a patient with tetralogy of Fallot and pulmonary atresia.

Hemodynamic Disturbances

The relation between resistances to blood flow from the ventricles into the aorta and into the pulmonary artery plays a major role in determining the hemodynamic and clinical picture.[8] Thus, the severity of obstruction to right ventricular outflow is of fundamental importance. When right ventricular outflow tract obstruction is severe, pulmonary blood flow is greatly reduced and a large volume of unsaturated systemic venous blood is shunted from right to left across the ventricular septal defect into the aorta. Severe cyanosis and polycythemia occur and the sequelae of systemic hypoxemia are prominent. At the opposite end of the spectrum, the term "acyanotic" tetralogy of Fallot is often used to describe an interventricular communication with relatively mild obstruction to right ventricular outflow and little or no venoarterial shunting. In many infants and children, the obstruction is initially mild but progressive, so that early in life pulmonary blood flow exceeds systemic flow and the clinical picture resembles simple ventricular septal defect.

Few children with tetralogy of Fallot remain asymptomatic or acyanotic; most are cyanotic from birth or cyanosis develops before 1 year of age. The earlier the onset of hypoxemia, the more severe the outflow tract stenosis. Dyspnea on exertion, clubbing and polycythemia are the rule. After exertion, children with tetralogy characteristically squat. An analogous posture may be beneficial in infancy; many of these cyanotic babies prefer to lie in a knee-chest position.

Figure 4.—Selective contrast injection into a systemic collateral artery visualizes the "gull-wing" configuration of hypoplastic right (rpa) and left pulmonary arteries **(arrows)** in a patient with tetralogy of Fallot and pulmonary atresia. (From Friedman[8]; reproduced by permission from WB Saunders Company.)

Episodic spells of intense, transient increases in cyanosis related to a sudden increase in venoarterial shunting and reduction in pulmonary blood flow usually have their onset between 2 and 9 months of age and constitute an important threat to survival. Attacks are not restricted to patients with severe cyanosis and are characterized by anxiety, hyperpnea and deepening cyanosis, progress to limpness and syncope and occasionally terminate in convulsions, cerebrovascular accidents and death. These spells result from an abrupt reduction in pulmonary blood flow.[8] This reduction is precipitated by an abrupt fall in systemic vascular resistance or an acute increase in right ventricular outflow obstruction (augmented contraction of the hypertrophied outflow tract muscle) or a decrease in right ventricular cavity volume due to tachycardia. The carbon dioxide partial pressure (P_{CO_2}) rises, while oxygen partial pressure (P_{O_2}) and pH fall. Treatment consists of administering oxygen, placing the child in the knee-chest position and administering morphine sulfate. Additional medications include intravenously given sodium bicarbonate to correct the acidemia, α-adrenergic-receptor stimulants such as phenylephrine hydrochloride or methoxamine hydrochloride to raise peripheral resistance and diminish right-to-left shunting and β-adrenergic-blocking agents that reduce cardiac sympathetic tone, depress cardiac contractility and increase right ventricular volume by reducing heart rate.

Preoperative Evaluation

Cardiac catheterization and selective angiocardiography are needed not only to confirm the diagnosis and assess the magnitude of right-to-left shunting but, most importantly, to establish the architecture of the right ventricular outflow tract, the pulmonary arterial branches and the anatomy of the coronary arteries.[3,12] Axial cineangiography, particularly using the sitting-up projection, facilitates evaluation of the pulmonary outflow tract and main branches. The preoperative assessment of tetralogy of Fallot with pulmonary atresia must include delineation of the arterial supply to both lungs by selective visualization of systemic collateral arteries. Pulmonary arteries may opacify only after the systemic collateral arteries are cleared of contrast material. Patients with pulmonary atresia should not be ruled out for intracardiac correction unless main pulmonary arteries are clearly inadequate.[4-7] Occasionally, injection of a contrast agent through a catheter in the pulmonary venous capillary wedge position is needed to visualize the pulmonary arteries.[6]

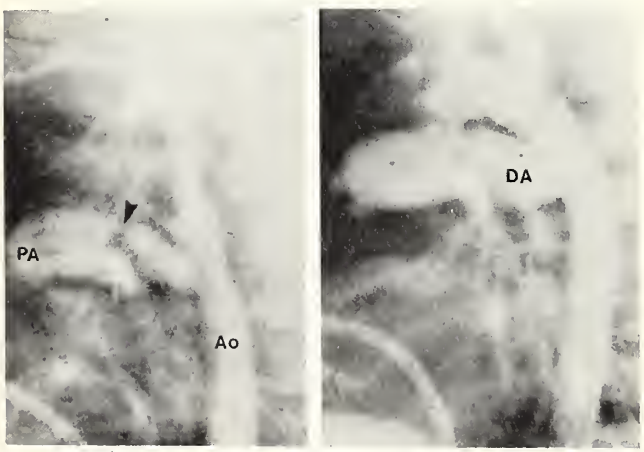

Figure 5.—Sequential aortograms before **(left panel)** and after **(right panel)** intravenous infusion of prostaglandin E_1 in a newborn with ductus arteriosis (DA)-dependent pulmonary blood flow and tetralogy of Fallot. The ductus is constricted in the left panel **(arrow)**, but dilated by the prostaglandin E_1 in the right panel. The dilatation of the ductus arteriosus provided more adequate pulmonary blood flow and improved oxygenation. PA = pulmonary artery, Ao = aorta

Management

Among the factors that complicate the management of patients with Fallot's tetralogy are erythrocytosis, iron deficiency anemia, coagulation disorders, infective endocarditis, paradoxic embolism, cerebral infarction or abscess and paroxysmal hypercyanotic spells discussed earlier. In infants with pulmonary atresia, cardiac catheterization is often done as an emergency. Because survival in this setting usually depends on patency of the ductus arteriosus, intravenous infusion of prostaglandin E_1 (0.1 mg per kg of body weight per minute) may dramatically reverse clinical deterioration and improve arterial blood gases and pH (Figure 5).[12-14]

Primary correction is advisable at some point in the natural history for almost all patients who have tetralogy of Fallot.[15] Early intracardiac repair, even in infancy, is currently advocated in most centers properly equipped for infant cardiac operations.[14] Successful early correction avoids progressive infundibular obstruction, acquired pulmonary atresia, delayed growth and development and complications due to hypoxemia and polycythemia. The size of the pulmonary arteries rather than the age or size of the infant or child is the most important determinant in establishing candidacy for primary repair. Pronounced hypoplasia of the pulmonary arteries is a relative contraindication for an early corrective surgical procedure. When this problem is present, a palliative operation designed to increase pulmonary blood flow is recommended and usually consists of a systemic arterial-pulmonary arterial shunt. Transventricular infundibulectomy or valvotomy are additional palliative procedures but are seldom used. Primary correction can then be carried out at a lower risk later in childhood or in adolescence.

Surgical Interventions—Palliative and Corrective

Hillel Laks, MD:* Tetralogy of Fallot exemplifies many of the challenges and advances in the surgical treatment of congenital heart disease.

History

In 1777 Sandifort,[16] studying an autopsied patient who had what came to be known as the tetralogy

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of Fallot, pointed out that the patent ductus arteriosus may have reduced cyanosis. A correlation of the degree of cyanosis with the amount of pulmonary blood flow was recognized by Helen Taussig,[17] who collaborated with Alfred Blalock to develop the subclavian-to-pulmonary artery shunt. This operation, first done successfully on November 29, 1944, was followed by the development of the Potts shunt,[18] the Glenn shunt[19] and the Waterston shunt.[20] In 1948 Brock[21] successfully applied a procedure, first proposed by Doyen in 1913,[22] in which a punch-type instrument was used to do an infundibulectomy.

Total correction of tetralogy of Fallot was first accomplished in 1954 by Scott and associates[23] using hypothermia and circulatory arrest. In 1955 Lillehei and co-workers[24] successfully corrected intracardiac defects using cross circulation. This pioneering work was advanced by Kirklin and colleagues,[25] Kay and associates[26] and others who established the current techniques of repair with cardiopulmonary bypass. With the advances in surgical technique and postoperative care, the mortality in tetralogy of Fallot has been greatly reduced in the past 25 years; intracardiac operation is now done in early infancy.

Palliative Versus Corrective Operation

The surgical treatment of tetralogy of Fallot has evolved from the period during which only palliative measures were available for increasing pulmonary blood flow to the current use of corrective surgical repair. As the results improved, correction was applied to younger infants, leading to considerable debate about the optimal timing for surgical treatment. Some prefer creation of a palliative shunt in infancy followed by correction at a later age.[27] Others recommend total correction in a symptomatic infant regardless of age.[28,29] Proponents of early correction point out that the mortality of the shunt procedure must be added to the mortality of subsequent repair.[28,30] In addition, the shunt may result in stenosis of the pulmonary artery and increased pulmonary vascular resistance; takedown of the shunt may complicate the corrective procedure. Early correction may avoid the deleterious effects of outflow tract obstruction on right ventricular function.[28,31]

Against early correction is the increased risk of operation in which there is a reported mortality of 25% to 67% in the first three months of life.[28,32] In contrast, palliative procedures can be done with a relatively low risk in patients under the age of 6 months.[33,34] Corrective operations undertaken in a child 1 or 2 years of age or older, with or without a palliative shunt, have a low risk of mortality.[27,32,33]

Our practice is similar to that proposed by Kirklin and associates[32] and takes into account the age of a patient and the anatomy of the lesion. In patients younger than 3 months of age a shunt is usually preferred. However, if the obstruction is predominantly due to a spastic infundibulum in a patient presenting with cyanotic spells, propranolol may be given until the age of 3 to 6 months at which time correction can be done. In patients between the ages of 3 and 6 months, the decision as to which procedure to use is based on the anatomy. If the obstruction is mainly infundibular, with a good-sized annulus and pulmonary arteries, correction is the procedure of choice. If the annulus and pulmonary arteries are small, a shunt operation is done because a transannular patch is not well tolerated in small infants. In patients older than 6 months, correction is done, if necessary, with a transannular patch.

Palliative Operation

The commonest form of palliation for tetralogy of Fallot is a systemic-to-pulmonary artery shunt.[35] Infundibular resection using a closed technique is no longer done. The Potts shunt has been largely abandoned because of a tendency to excessive pulmonary blood flow and the difficulty in takedown of the shunt during a corrective procedure.[36] The Waterston shunt is still used by some, particularly in small infants. It is also associated with excessive pulmonary blood flow, however, and frequently results in pulmonary artery constriction requiring reconstruction of the artery during a corrective surgical procedure.[37] The shunt of choice, even in a neonate, remains the Blalock-Taussig shunt.[33] Excellent results have also been obtained with polytetrafluoroethylene grafts placed between the subclavian artery and the pulmonary artery.[38]

In small infants with a pulmonary artery-to-aorta ratio of less than 0.3, Tucker and associates[15] inserted a pericardial outflow-tract patch without closing the ventricular septal defect; among nine infants one death occurred. Further experience is needed to prove that this procedure can be done with results comparable with the palliative shunt.

Results of Palliative Shunts

The younger a patient, the greater the risk with a palliative shunt. One series with excellent results reports an operative mortality of 6% in infants 1 month of age, 4% in those at 3 months, 3% at 6 months and 2.5% at 12 months.[34] The longevity of palliation after a shunt procedure varies according to the age at which the operation is done and the type of shunt. For the Blalock-Taussig and polytetrafluoroethylene graft shunts created in the first months of life, the duration of palliation seems to be about 18 months. In an older child, many years of palliation can be achieved with a Blalock-Taussig shunt.[39]

Corrective Operation

The corrective procedure is done using a median sternotomy incision. In female patients a submammary skin incision with a median sternotomy may be used.[40] In infants weighing less than 6 kg, the procedure is done during deep hypothermia and circulatory arrest. The aorta is cannulated directly, and if circulatory arrest is to be used, a single cannula is placed in the right atrium. If continuous bypass is used, the superior and

inferior venae cavae are cannulated separately through the right atrium and snared. A prior Blalock-Taussig shunt is ligated immediately before instituting bypass. If a Potts shunt is present, it is occluded by finger pressure while cardiopulmonary bypass is instituted and the blood rapidly cooled. The left pulmonary artery is then opened longitudinally, and, if necessary, under circulatory arrest the shunt is closed and the pulmonary artery reconstructed.[41] The Waterston shunt is taken down after commencing bypass and cross clamping the aorta.[42] The pulmonary artery may need reconstruction with a pericardial patch.

Cardiopulmonary bypass is instituted using moderate hemodilution (hematocrit 25%), with blood cooled to 20°C or 28°C, depending on the age of the child. In smaller infants, lower temperatures are used and the repair done either under circulatory arrest or under low flows to achieve optimal visualization of the operating field. The atrial septum is inspected and a patent foramen ovale or atrial septal defect closed either through the tricuspid valve or through a separate right atrial incision.

The incision in the right ventricle (Figure 6)[43] depends on the anatomy delineated by angiography. If it is clear that a transannular path will be needed, a vertical incision is made in the right ventricular outflow tract and, after inspection and measurement of the annulus, the incision is extended to the bifurcation of the pulmonary artery. If the pulmonary arteries and annulus are adequate and the obstruction is mainly infundibular, an oblique or transverse incision is made in the right ventricular outflow tract, avoiding large coronary artery branches. If it is not clear whether a transannular patch will be needed, a vertical or slightly oblique incision is made, permitting extension across the annulus if necessary.

In the presence of an anomalous left anterior descending coronary artery arising from the right coronary artery (in about 5% of patients with tetralogy of Fallot), special considerations apply (Figure 6). If the annulus does not need to be enlarged, a transverse incision can be made below the coronary artery, or a vertical incision can be made and the artery mobilized to permit insertion of the tip of the subannular patch below the anomalous vessel. If the annulus is restrictive, a valved conduit is used to bypass the obstruction.

The technique for intracardiac repair is described and shown in Figure 7. After resection of the outflow tract obstruction, including the septal and parietal bands and a portion of the crista supraventricularis, attention is turned to the pulmonary valve. If there is fusion of the commissures, this can be incised carefully from below. The annulus is measured with Hegar dilators and its diameter is compared with the normal valve sizes prepared by Pacifico and associates.[44] If the diameter is less than the 50% confidence limits for the patient's age, a transannular patch will be needed; in this case the incision is extended across the annulus to the bifurcation of the pulmonary artery. The ven-

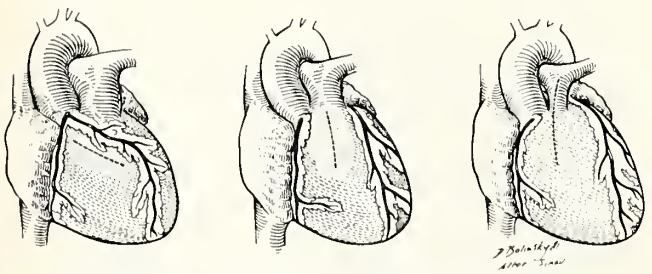

Figure 6.—Three right ventricular incisions used in the repair of tetralogy of Fallot. **Left,** An oblique or transverse incision is used if angiograms show that a transannular patch will not be needed because the obstruction is mainly infundibular and the pulmonary valve and annulus are not narrowed. This incision is also chosen in the presence of an anomalous left anterior descending coronary artery arising from the right coronary and when the pulmonary annulus does not need enlargement. **Middle,** A vertical incision extending up to, but not across, the annulus is used when it is uncertain whether a transannular patch will be needed. **Right,** When the annulus needs enlargement, the incision is extended up to the bifurcation of the pulmonary artery and a transannular patch inserted. (From Laks[43]; reproduced by permission from Appleton-Century-Crofts.)

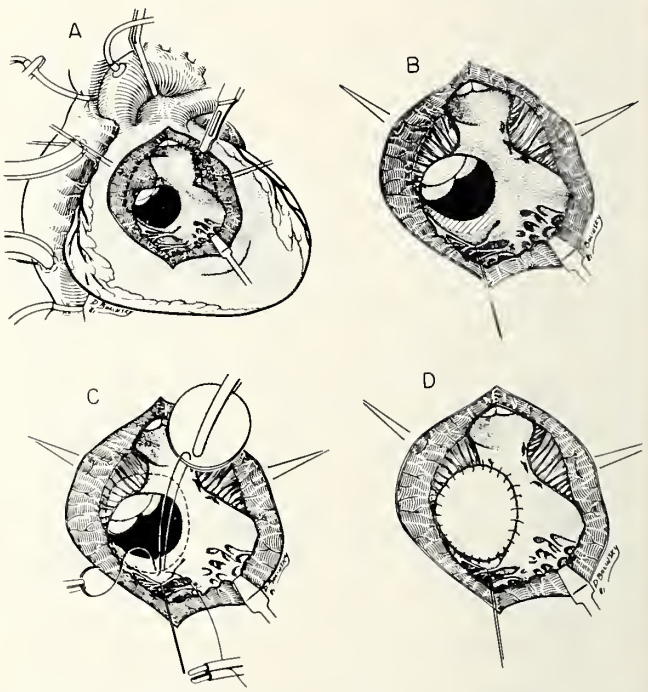

Figure 7.—Technique of repair for tetralogy of Fallot. **A,** The ventricular septal defect is exposed through a vertical right ventriculotomy. The dotted line indicates the resection of the parietal and septal bands. Restricting muscle bands are divided. **B,** Exposure of the ventricular septal defect. The aortic valve is clearly seen. The area of the conduction tissue, which should be avoided, is indicated by the cross-hatching. **C,** A running suture line of Prolene (Ethicon Inc, Somerville, NJ 08876) is used to close the defect. The suture line is below the area of the conduction tissue and continues to the septal leaflet of the tricuspid valve and aortic annulus. The dotted line indicates the patch of the suture line. **D,** The double-velour Dacron (CR Bard Laboratories, Box M, Billerica, MA 01821) patch is shown in position, with the suture line completed on the crista supraventricularis. (From Laks[43]; reproduced by permission from Appleton-Century-Crofts.)

tricular septal defect is then closed (Figure 7), care being taken not to damage the conduction tissue in the posteroinferior corner of the defect. The incision in the outflow tract is then closed (Figure 8). We usually use pericardium reinforced with a Dacron mesh for the outflow tract patch. If pericardium is not available, a preclotted woven Dacron graft is used for this purpose.

After removing the patient from cardiopulmonary bypass, the right ventricular and pulmonary artery pressures are measured. If the ratio of right ventricular-to-left ventricular systolic pressure is greater than 0.65 and the pulmonary artery pressure less than 25 mm of mercury, bypass is reinstituted and the obstruction relieved by a transannular patch. Oxygen saturations are also determined to exclude a residual intracardiac shunt.

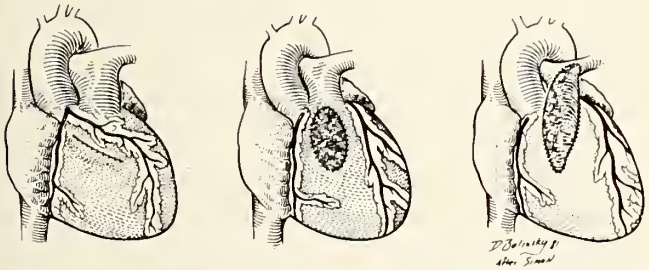

Figure 8.—Closure of the incisions. **Left,** The oblique or transverse incision is closed primarily with a double suture line. **Middle,** The vertical incision is closed with a subannular patch to enlarge the infundibular outflow tract. **Right,** The transannular incision is closed with a patch extending up to the bifurcation of the pulmonary arteries. (From Laks[43]; reproduced by permission from Appleton-Century-Crofts.)

Results of Corrective Operation

Mortality. Mortality accompanying repair of tetralogy of Fallot has decreased considerably during the past ten years. In patients younger than 1 year of age, mortality has been reported as high as 14%[25] and is higher in infants younger than 3 months of age.[15,28,32] One series of patients younger than 2 years of age had a mortality of 5%[29]; in another series the mortality among patients older than 1 year of age was 1.6%.[27]

Morbidity. Permanent heart block is now uncommon and occurs in less than 1% of surgically treated cases of tetralogy of Fallot. The presence of right bundle branch block and left anterior hemiblock may presage complete heart block.[45] Ventricular irritability may occur and cause late sudden death, as discussed later.

Residual lesions. These are discussed below, as are the long-term results of surgical correction.

Complex Tetralogy of Fallot

Under this broad term are included patients with virtual pulmonary atresia, absent pulmonary valve,[46] an atrioventricular canal defect combined with a tetralogy,[47] multiple intramuscular ventricular septal defects, a single pulmonary artery, well-developed systemic

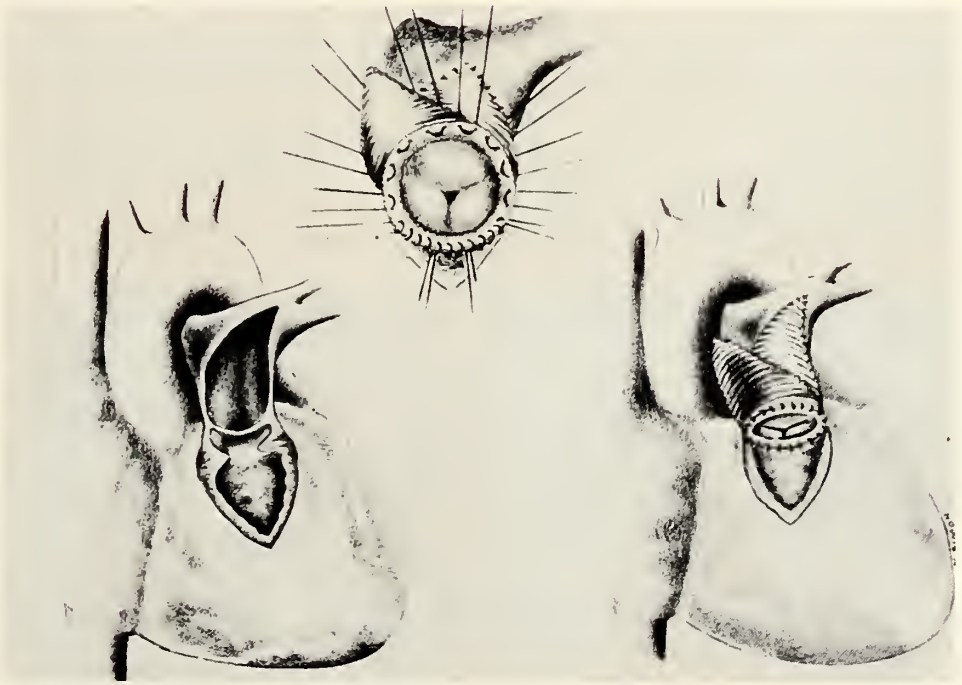

Figure 9.—Operative technique for pulmonary valve insertion beneath an outflow-tract patch. On the left, the incision extends to the bifurcation of the pulmonary artery. The inset shows the continuous sutures posteriorly and the interrupted suture line anteriorly through the patch. On the right, the valve is seen sutured beneath the patch before the completion of the patch suture line to the edges of the right ventricular incision. (From Laks[43]; reproduced by permission from Appleton-Century-Crofts.)

arterial collaterals, an aorticopulmonary window,[48] bifurcation or distal pulmonary stenosis, Epstein's anomaly and pulmonary stenosis due to previous Potts or Waterston shunts.

Tetralogy of Fallot with a single pulmonary artery. It is usually the left pulmonary artery that is absent, the left lung being supplied by systemic arterial collaterals. Whether or not a valved conduit rather than a transannular patch should be used to relieve the outflow obstruction has been considered.[49,50] A patch without a valve may be well tolerated in the absence of pulmonary hypertension or distal stenosis and if the pulmonary artery is of good size. If these conditions do not pertain, a bioprosthetic valve (either a glutaraldehyde-preserved porcine or a bovine pericardial valve) should be inserted. A valved conduit may also be used,[48] or a valve can be placed beneath an outflow-tract patch (Figure 9).[41]

Tetralogy of Fallot combined with atrioventricular canal. Pacifico and colleagues[47] studied this combined lesion in ten patients and reported good surgical results. The complete atrioventricular canal is treated in the usual fashion. Particular attention should be paid to obtaining competent mitral and tricuspid valves because tricuspid regurgitation is not tolerated well in the presence of pulmonary regurgitation or obstruction. The outflow-tract obstruction is relieved by the usual techniques. If a transannular patch is needed, a pulmonary valve should be inserted beneath the patch.

Pulmonary valve insertion. Although the severe pulmonary regurgitation accompanying a transannular patch is usually tolerated well, there is a group of patients in whom pronounced right ventricular failure develops.[51,52] Within this group are patients who have distal pulmonary stenosis, increased pulmonary vascular resistance, associated tricuspid regurgitation, absent pulmonary valve, virtual pulmonary atresia and a single pulmonary artery. Additionally, there are patients in whom some years after tetralogy repair a dilated, poorly contractile right ventricle develops. In many of these patients valved conduits have been used. We prefer placing a porcine valve in the right ventricular outflow tract beneath a patch, which avoids compression of a conduit by the sternum, and permits insertion of a larger sized valve.[53]

Absent pulmonary valve syndrome. The anatomy of absent pulmonary valve syndrome consists of a ventricular septal defect, a small pulmonary valve annulus with no valve cusps and aneurysmal dilatation of the central pulmonary arteries with small peripheral pulmonary arteries (Figure 10).

About 25% of these patients present in infancy with respiratory problems due to bronchial compression by the dilated pulmonary arteries. In others, the shunt is predominantly left to right and cyanosis is not a major feature. Because of the combination of pulmonary stenosis and regurgitation, a prominent precordial to-and-fro murmur is heard.

Studies by angiography show the main pulmonary arteries to be aneurysmally dilated and the distal branches small. The pulmonary annulus is smaller than normal and the left pulmonary artery may be missing.[54]

Surgical treatment. The ventricular septal defect is closed in the usual fashion. A valve should be inserted in the outflow tract because severe pulmonary regurgitation combined with aneurysmally dilated pulmonary arteries results in a low output state postoperatively. The valve may be placed beneath an outflow-tract patch (Figure 9). In infants who have bronchial compression, the aneurysmally dilated pulmonary arteries can be surgically narrowed.[55]

Benefits and Complications of Shunt Operations; Residua and Sequelae of Intracardiac Repair

JOHN S. CHILD, MD:* Residua and sequelae after a cardiac operation have resulted in a new and growing patient population—those with postoperative congeni-

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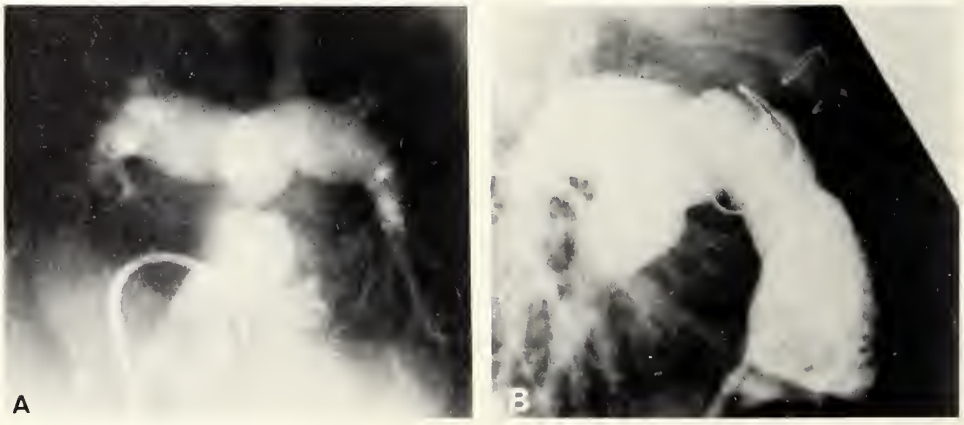

Figure 10.—Absent pulmonary valve. **A,** An anteroposterior right ventriculogram of an 8-month-old child, showing the narrowed annulus and the aneurysmally dilated main right and left pulmonary arteries with small peripheral arteries. **B,** A postoperative lateral angiogram, showing the repair with insertion of a 21-mm porcine valve beneath an outflow-tract patch. (From Laks[13]; reproduced by permission from Appleton-Century-Crofts.)

tal heart disease.[56] Patients born with tetralogy of Fallot 15 years ago had an 85% probability of being alive today and a 75% probability of living to the fourth decade.[57] Patients born today with the same condition have an even better prognosis. However, operation leaves behind obligatory abnormalities, some trivial, others serious. Proper care of adults with postoperative congenital heart disease requires knowledge of the presence, type and extent of these postoperative residua and sequelae.

Palliative Shunts

A systemic-pulmonary arterial shunt created surgically[17,18,20,58] was the first successful palliative treatment for tetralogy of Fallot. Benefits result from increased pulmonary arterial blood flow with enhanced systemic oxygen saturation; symptomatic improvement often is dramatic. Growth of underdeveloped pulmonary arteries can occur, facilitating subsequent intracardiac repair. Detrimental effects include excessive pulmonary blood flow, congestive heart failure and pulmonary vascular disease.[36,59-66] Acquired pulmonic atresia is an occasional late complication.[67] Pulmonary vascular disease is rare after Blalock-Taussig anastomoses (subclavian-pulmonary artery shunt),[59] at least for seven years.[66] The direct aortopulmonary arterial shunts (Potts, Waterston-Cooley[18,20,58]) show a higher incidence of pulmonary vascular disease, particularly the Potts procedure. Clinical findings of an excessively large anastomosis (thus warranting concern that pulmonary vascular disease may develop) include minimal or absent cyanosis; a short, low-pitched, coarse continuous murmur; progressive cardiac enlargement; increasing prominence of the pulmonary trunk and pulmonary arterial vascularity, and the appearance and progression of electrocardiographic evidence of left ventricular hypertrophy.[64] In patients with these findings, subsequent shortening or disappearance of the continuous murmur is a sign of pulmonary vascular disease.[57]

Blalock-Taussig Shunt

After a Blalock-Taussig shunt, in 4% to 6% of patients, brain abscesses develop and 2% to 5% have cerebrovascular accidents.[68,69] A subclavian steal means that collateral flow to the arm (on the side of the anastomosis) via the ipsilateral vertebral artery shunts ("steals") blood from the brain.[70] Growth of the arm on that side may be impaired, though patients are rarely aware of this. Endocarditis has been reported in as many as a third of patients before intracardiac repair.[57,71] Finally, because the size of the Blalock-Taussig anastomosis does not always grow with the patient, the effect of palliation decreases.[72]

Potts Anastomosis

Pulmonary overcirculation due to the Potts anastomosis (descending aortopulmonary arterial shunt) usually occurs in children, less often in adults.[57] On the other hand, pulmonary vascular disease is seen more frequently in adults; this sequela of operation correlates directly with the size and duration of the anastomosis.[36] Such patients are also at risk for infective endocarditis and cerebrovascular accidents.[57,70] The surgical mortality of intracardiac repair after Potts anastomosis is greater than with other types of shunts and higher than for primary intracardiac repair.[57] In addition, closure of the Potts anastomosis is technically difficult, prolonging the intracardiac repair and increasing the risk.

Waterston-Cooley Anastomosis

The Waterston-Cooley procedure (anastomosis of ascending aorta to right pulmonary artery) risks fewer sequelae than the Potts. The most frequent major complication is kinking and distortion of the right pulmonary artery, relief of which may require special reconstruction at the time of intracardiac repair.[70] Furthermore, when blood flow is restricted to one lung, the opposite lung is at increased risk of pulmonary vascular disease due to excessive blood flow.[73,74]

Intracardiac Repair

Direct intracardiac repair of tetralogy of Fallot, available for more than two decades, has evolved rapidly.[75,76] With the surgical technique now relatively standardized, attention has focused on late clinical and hemodynamic residua and sequelae and operative factors governing late morbidity and mortality.[77] Among these factors are the timing of operation, indications for a transannular patch, identification of patients at risk for late postoperative sudden death and the long-term right ventricular response to postoperative pulmonary valve incompetence.[78]

Let us now consider the sequelae of right ventriculotomy: of intraventricular closure of the ventricular septal defect; reconstruction of the right ventricular outflow tract; prosthetic materials, and residua that include right ventricular outflow obstruction, myocardial hypertrophy and right ventricular function. Complications will not be discussed.

Postoperative Sequelae

Right ventriculotomy. Incision of the right ventricular outflow tract sometimes results in ventricular aneurysm, which rarely is obvious and dramatic.[56] Of more concern is the effect of ventriculotomy on the long-term performance and functional reserve of the incised ventricle.[56,70]

During ventriculotomy injury to an anomalous coronary artery must be avoided.[79] The anterior descending or conal arteries have occasionally been injured or transected.[80]

Endocardial fibroelastosis, not only in chambers handled by the surgeon, but also in other chambers, is believed to be due to interrupted lymph drainage.[80] This sequela is not necessarily innocuous and may be responsible for late myocardial dysfunction.[80]

Conduction disturbances. Right bundle branch block, common after repair of tetralogy of Fallot.[81,82] is probably functionally benign.[70] The right bundle branch block may be due to interruption of distal or

terminal arborization of the right bundle (ventriculotomy per se) or of the proximal right bundle (repair of the ventricular septal defect).[56,83] A surface electrocardiogram is inadequate for determining the location of right bundle branch block, but intraoperative endocardial and epicardial mapping can establish the site.[84]

Bifascicular block (right bundle branch block with left anterior fascicular block) sometimes accompanies an operation (reported incidence 7% to 25%).[85-89] Most cases occur at the time of operation and persist. In some patients, the left anterior fascicular block is transient[90] but in others appears late postoperatively.[83] The prognosis of bifascicular block in this setting is controversial,[81-83] though the current consensus[77,87,88,90-93] is that sudden death due to subsequent high-degree heart block is uncommon, if not rare. Late complete heart block now occurs in 1% to 2% of patients who had intracardiac repair of Fallot's tetralogy.[85,94] The heart block can be temporary (hours to weeks in duration) or permanent and may be immediate or late (up to 14 years) postoperatively.[95-97]

The diagnosis of trifascicular conduction defects cannot be made with assurance by standard surface electrocardiography.[98] A prolonged His bundle-to-ventricle interval in the presence of right bundle branch block (with or without left anterior fascicular block) indicates infra-Hisian and usually trifascicular block, and sets the stage for subsequent complete heart block and slow ventricular escape rhythms.[99]

Ventricular arrhythmias. Until recently, sudden death after intracardiac repair of tetralogy of Fallot was ascribed to high-degree heart block (see above). This may occasionally be the case, but of equal or greater importance is electrical instability of the incised right ventricle.[77,93,100-102] Premature ventricular contractions are ominous after intracardiac repair.[57,93] Garson and associates[93] noted that 38% of their patients with premature ventricular contractions died suddenly. With exercise, especially in the postexercise recovery period, the incidence of premature beats increases (23%) and may culminate in ventricular tachycardia.[103] The most important correlation with premature ventricular contractions is elevated right ventricular systolic or end-diastolic pressure, or both.[93] The origin of inducible recurrent sustained ventricular tachycardia has been located in the right ventricular outflow tract.[83] The ventriculotomy scar coupled with increased myocardial oxygen demands of a right ventricle laboring under inadequate relief of afterload may provoke premature beats that deteriorate into sustained repetitive firing (ventricular tachycardia or fibrillation).[93] Exercise testing and ambulatory taped electrocardiography are desirable after intracardiac repair. Frequent premature beats or repetitive beats require antiarrhythmic therapy and consideration of cardiac catheterization. Reoperation for relief of significant right ventricular pressure overload might diminish the frequency and risk of premature ventricular contractions.[57] At reoperation, intraoperative endocardial mapping and resection of the reentrant pathways in offending ventricular scar should further reduce the likelihood of spontaneous ventricular tachycardia.[83]

Pulmonary regurgitation. Repair of obstruction to right ventricular outflow may leave behind pulmonary valve regurgitation (Figure 11).[56] The murmur of low pressure pulmonary regurgitation[104] is audible in up to 75% of patients after repair.[70] Long-term effects of this volume overload are uncertain.[105] Neither is it clear how well an initially thick-walled, relatively less compliant right ventricle responds if relief of obstruc-

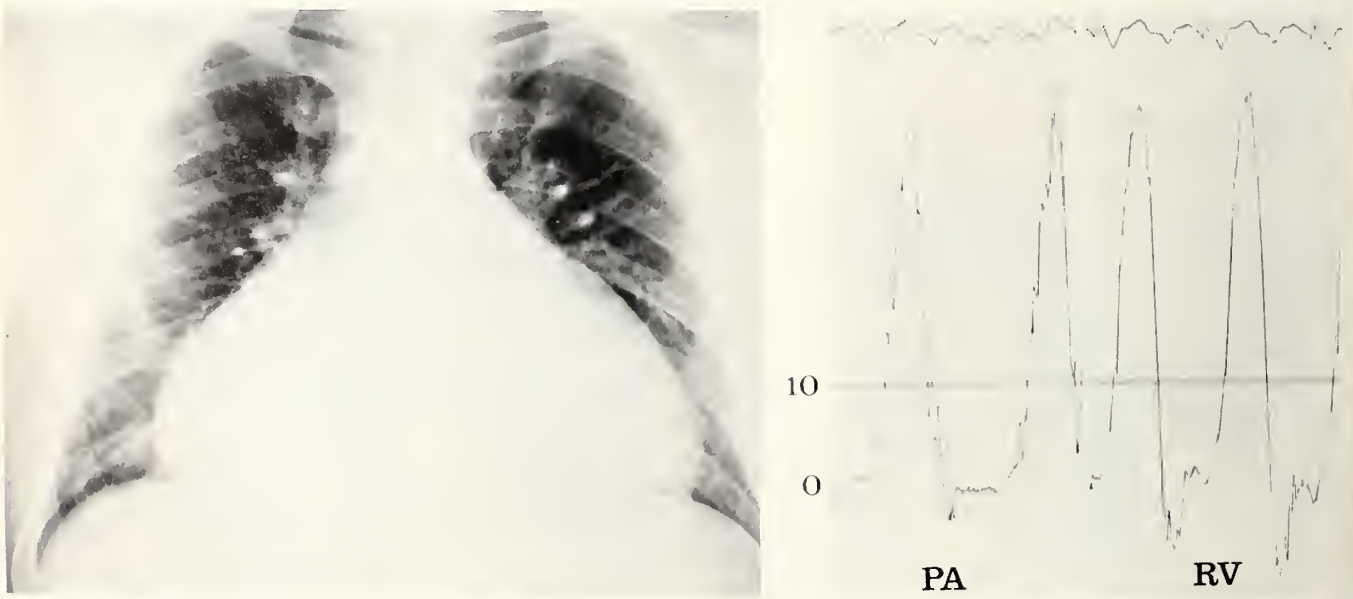

Figure 11.—Chest roentgenogram **(A)** and right heart pressure pulses **(B)** in a 30-year-old man who at 10 years of age underwent primary intracardiac repair for tetralogy of Fallot. Twenty years after operation severe pulmonary regurgitation culminated in right ventricular failure, tricuspid regurgitation and atrial flutter. The chest x-ray study shows massive cardiomegaly due to right atrial and right ventricular dilatation. The pulmonary arterial (PA) and right ventricular (RV) pressure pulses show no obstruction, identical diastolic pressures (free pulmonary regurgitation) and an early diastolic dip in the RV.

tion suddenly converts severe afterload (pressure) into moderate to pronounced preload (pulmonary regurgitation). The response of the ventricle is further complicated if repair requires not merely ventriculotomy but also an outflow or transannular patch. Thus, postoperative results depend in large part on the amount of reconstruction to which the right ventricular outflow tract is subjected[106] and the degree of residual obstruction and obligatory pulmonary regurgitation. Hemodynamic[106,107] and clinical data[70,77] indicate that most patients tolerate pulmonary incompetence well and that their exercise tolerance remains adequate *provided* there is no significant residual outflow-tract obstruction. Nonetheless, in patients who have isolated pulmonary regurgitation, late postoperative right ventricular failure sometimes develops (Figure 11).[108,109] Severe pulmonary regurgitation is associated with an elevated right ventricular end-diastolic pressure[109] exaggerated by exercise[70] or aggravated by branch stenoses of the large pulmonary arteries.[110-112] Associated tricuspid incompetence due to right ventricular failure is a serious sequela.[82,105,113]

Prosthetic Materials

Prosthetic materials used in repair include patches, artificial valves and extracardiac conduits. Follow-up studies for more than 20 years of patients in whom synthetic patches were used for closure of the ventricular septal defect, and in whom synthetic onlay or transannular patches were used for repair of the right ventricular outflow tract, have shown no significant cause for concern about durability.[77,114] However, insertion of pericardium as patch material for a ventricular septal defect has resulted in aneurysmal dilatation of the patch.[115] The early use of the Ivalon sponge was sometimes followed by reestablishment of the septal defect; occasionally aneurysms developed when this material was used as a patch for the right ventricular outflow tract.[114]

Durability, thrombogenicity, hemodynamic adequacy and a continuing threat of infective endocarditis remain concerns in the selection and implantation of prosthetic valves. Fortunately, few patients need insertion of a prosthetic pulmonary valve even when their native valve is nonfunctional after repair.[77]

Use of extracardiac conduits has made feasible the surgical correction of tetralogy of Fallot with pulmonary atresia[116]; an optimal conduit, however, is not yet available. Calcification of aortic homografts,[117] degeneration of synthetic or heterograft valves within a conduit and progressive proliferative fibrotic peel of a lumen limit the long-term outlook with current materials.[118,119]

Postoperative Residua

Right ventricular outflow gradient. Causes of residual postoperative outflow gradients include inadequate relief of subvalvular obstruction, stenosis of the valve or main pulmonary artery (at the site of a patch insertion) or stenosis of pulmonary arterial branches.[57] Ruzyllo and co-workers[106] found that only 43% of 221 catheterized postoperative patients had a right ventricular-pulmonary artery pressure gradient of less than 20 mm of mercury; however, most patients with less satisfactory relief of obstruction had few or no symptoms. Persistent stenosis postoperatively relates chiefly to the structure of the preoperative obstruction.[72] If only infundibulectomy is needed, 65% of patients have less than 20 mm of mercury gradients, but if more complex reconstruction is required, only 35% attain near complete relief of stenosis. When the postoperative right ventricular-to-left ventricular pressure ratio is more than 0.65[77] or right ventricular systolic pressure is more than 60 mm of mercury[57,106,107] (particularly in those without patch reconstruction), risk of right ventricular hypertension increases and reoperation is needed to reduce the risk of sudden death. Outflow gradients may develop or increase significantly during exercise.[120] The risk of infective endocarditis remains.

Reoperation for residua. Although in most patients the symptomatic result from intracardiac repair is satisfactory, the aforementioned points underscore that important residual lesions may remain. Symptomatic as well as asymptomatic patients with significant residual abnormalities should be recatheterized, even though firm criteria for reoperation are difficult to establish.[121-123] The most common residuum needing reoperation is the right ventricular outflow gradient. Less commonly, valve replacement for pulmonary regurgitation or reconstruction for tricuspid insufficiency is necessary.[77,105,121,122] Reoperation is occasionally needed to excise a right ventricular outflow aneurysm. Fortunately, reoperation is associated with a relatively low risk, probably no greater than that for the initial repair.[77,105,121,122,124]

Myocardial hypertrophy and ischemia. When the fetal right ventricle continues to function as a systemic pump after birth, as in cyanotic tetralogy of Fallot, right ventricular wall growth keeps pace with left ventricle and septum, and long-term function of the right ventricle is good.[125] Nevertheless, an operation done early in the natural history has important long-term objectives: normalization of ventricular mass, preservation or restoration of normal function per unit mass and to assure normal life expectancy. After intracardiac repair of Fallot's tetralogy, however, right ventricular ejection fraction during exercise may be depressed,[126-128] and abnormalities of resting right ventricular volume and ejection fraction occur in patients with large outflow patches.[127]

A continually "underloaded" left ventricle in cyanotic tetralogy of Fallot increases its volume and mass after intracardiac repair. Mild to moderate impairment of left ventricular function persists in patients not corrected in early childhood, especially those with severe prolonged cyanosis.[93,127,129] Long-term exposure of the myocardium to polycythemia and hypoxia results in myocardial ischemia. Fortunately, recent data[113,128,130,131] on adolescents and adults show normal

resting and exercise left ventricular function in most cases.

Functional responses to exercise. The average exercise capacity of postoperative patients with tetralogy of Fallot is less than normal, but individual scores vary widely even for patients with seemingly similar surgical results.[103,120,132] In these cases, exercise performance is modified by varying degrees of impaired chronotropy and reduced stroke volume.[132] As expected, patients with excellent results (normal right ventricular pressure, no outflow patch and no residual shunt) show the best functional results. Furthermore, patients who undergo intracardiac repair early in life seem to have less depression of cardiac performance with exercise[103,132] or afterload stress.[133]

Conclusion

DR PERLOFF: And now a look toward the future. Surgical improvements continue—perhaps not in quantum leaps—though most of the major dramatic breakthroughs may well have been achieved. Nevertheless, there will be a constant search for improved prosthetic materials, especially cardiac valves and conduits,[114] refinement of techniques currently used, development of new techniques and continued attention to intraoperative myocardial preservation (cardioplegia, reperfusion and so forth). In this discussion, I shall focus on some important concerns in addition to, though not necessarily apart from, the surgical improvements alluded to above; I will not confine myself to the tetralogy of Fallot and its variations. I shall briefly comment on defects uncorrected after primary repair, sequelae of ventriculotomy, electrophysiologic sequelae and residua in addition to those imposed by the ventriculotomy incision itself, valvular anatomic residua and sequelae, elevated pulmonary vascular resistance, the development and regression of increased ventricular mass and the genetics of women who survive to childbearing age after operation for congenital heart disease.[56]

Certain primary anatomic repairs leave behind uncorrected defects (residua) that may not assume physiologic importance for many decades.[56] I speak of a functionally normal bicuspid aortic valve after repair of coarctation of the aorta, mitral valve prolapse persisting after closure of an ostium secundum atrial septal defect and a cleft but competent mitral valve with a repaired ostium primum atrial septal defect.[56] In addition to the important long-term natural history of a functionally normal bicuspid aortic valve after coarctation repair, several other late postoperative concerns possibly beset these patients, namely, regulation of systemic arterial pressure, premature coronary artery disease, postoperative central nervous system complications and abnormalities of the mitral apparatus.[56] In ostium secundum atrial septal defect, the natural history of mitral valve prolapse is unclear and awaits more secure identification of *pathologic* mitral prolapse (a true developmental connective tissue fault of leaflets, annulus and chordae tendineae).[134] Regarding the cleft but competent mitral valve after primary anatomic repair of partial endocardial cushion defect, it is not yet known how susceptible that valve is to infective endocarditis or how well the leaflets, with their abnormal chordal arrangements, will retain competence during changes in left ventricular geometry in adult life.[56]

Incision of the right ventricle is used for intracardiac correction of the host of congenital lesions, one of which is the tetralogy of Fallot (see Dr Laks's remarks above). Two possible postoperative sequelae of ventriculotomy concern us, namely, the effects on ventricular electrical activity[83,85,102] and the effect on long-term myocardial contractility of the incised ventricle.[56] In addition to improving our knowledge of factors that result in electrical instability of an incised ventricle, certain important electrophysiologic sequelae follow intracardiac repair, both intra-atrial and intraventricular.[56,83] Complex intra-atrial corrections, such as Mustard's or Senning's baffle for complete transposition of the great arteries, may be followed years later by sinus node dysfunction, abnormalities of atrioventricular-node conduction, atrial flutter or atrial fibrillation.[56] Right ventriculotomy per se is responsible for two electrophysiologic concerns—electrical instability of the incised ventricle and alteration in the sequence of right ventricular activation (peripheral).[83] Intracardiac repair sometimes results in interruption of the left anterior fascicle and proximal right bundle branch (bifascicular block). Prolonged His-Purkinje conduction time (trifascicular disease) has been identified after intracardiac correction of tetralogy of Fallot.[56,83,84]

Valvular anatomic residua are necessarily present after direct repair of simple discrete valvular aortic stenosis and simple valvular pulmonic stenosis. Such valves are not morphologically normal even though the gradients may be abolished. Also, an abnormal aortic valve (with aortic regurgitation) is often left behind after uncomplicated repair of discrete subvalvular aortic stenosis.[56]

Pulmonary hypertension or, more precisely, increased pulmonary vascular resistance in operative risk and late postoperative results, continues to be a problem.[135] In certain disorders there is a special proclivity for progressive pulmonary vascular obstruction to develop, for example, endocardial cushion defects with Down's syndrome and complete transposition of the great arteries.[135] Our present knowledge of the pulmonary vascular bed has now been extended considerably beyond the pulmonary vascular disease described earlier.[135] I speak of the new approaches to morphologic analysis of this vascular bed in patients with congenital heart defects, that is, the abnormalities of arterial remodeling and growth that have been detected and quantified in early infancy.[136]

An increase in ventricular mass is perhaps the most important structural adaptation of heart muscle to overload.[125] In addition, hypoxia results in cell replication in an immature heart.[125] Both the development and regression of increased ventricular mass are being

studied. A number of points are under scrutiny, namely, normal ventricular growth (in embryo, fetus, neonate and child); the response to workloads (hemodynamic stress) and hypoxia; the cell responses of hyperplasia (increase in cell number), hypertrophy (increase in cell size) and the type of cell (muscle or connective tissue); the age or maturity of the myocardium when hemodynamic or hypoxic stress is imposed, and the biochemistry, ultrastructure and functional morphology (modeling) of the ventricles in response to volume or pressure overload.[125] The desirable physiologic adaptations to workloads must be characterized further and the transition from physiologic to pathologic states established. Regression of increased ventricular mass is being studied at the cell level (hypertrophy versus hyperplasia; muscle cells versus connective tissue cells) and at the organ level.[125] The requirements for maintaining or establishing normal ventricular function after removal of overload must be defined, together with variables such as the type and duration of preoperative hemodynamic stress, the right versus the left ventricle and the relative rates of contractile protein synthesis and degradation.[125]

There has long been concern that the growing number of postoperative congenital cardiac patients reaching childbearing age will produce a higher incidence of offspring who have congenital anomalies of the heart or circulation.[56] Accordingly, genetic investigations are being carried out.[137] Results at present show that women with congenital heart disease are at increased risk of giving birth to children with congenital cardiac anomalies, a risk not significantly affected by surgical repair and one that is considered to be of genetic importance.[137]

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Hypoglycemia: A Pitfall of Insulin Therapy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Diabetes mellitus is a disease that is often extremely difficult to treat effectively. That is true despite almost 60 years of experience with insulin. For this Medical Staff Conference we have asked Dr Kenneth R. Feingold from the Metabolism Section of the Department of Medicine at the Veterans Administration Medical Center to discuss one of the important complications of insulin therapy, that of hypoglycemia.*

DR FEINGOLD:† In the past several years, there have been increasing efforts to more vigorously reduce blood glucose levels towards normal in patients who have diabetes mellitus, in the hope that this will prevent or delay the microvascular and neurologic complications associated with diabetes.[1,2] The introduction of "tight" metabolic control carries with it the potential for serious hypoglycemic side effects. In this presentation, I will discuss the dangers of hypoglycemia in insulin-treated diabetic patients and will describe techniques to diagnose and prevent this complication. Hypoglycemia also occurs in a significant number of patients taking oral hypoglycemic agents[3] but I will focus on hypoglycemia that occurs due to insulin treatment.

While all diabetologists agree on the goal of normalizing blood glucose levels in diabetic patients, achieving this goal in practice is frequently impossible with the currently available therapies. A number of recent studies show very impressive degrees of metabolic control with intensified conventional therapies or continuous insulin infusion pumps. These results, however, were obtained in a selected, highly motivated subgroup of patients and do not necessarily represent the norm. Attempts to vigorously control blood glucose levels in some patients may result in serious hypoglycemia and therefore the goal of normal blood glucose concentrations must be balanced against the possible development of serious iatrogenic hypoglycemic side effects.

How Common Is Hypoglycemia in Insulin-Treated Diabetic Patients?

Hypoglycemia is a frequent complication of insulin therapy for diabetes. The frequency of hypoglycemia varies greatly from study to study, in part due to the intensity with which hypoglycemic episodes are searched for. Nocturnal hypoglycemia is often unrecognized by both patients and physicians. In one study in which blood glucose levels were monitored hourly overnight, 22 of 39 poorly controlled insulin-treated diabetic patients had nocturnal hypoglycemia.[4] In 17 of the 22 patients, the nocturnal hypoglycemia lasted for more than three hours.[4] In another similar study, 6 of 34 diabetic patients treated with insulin had asymptomatic nocturnal hypoglycemia and 5 of 34 had symptomatic hypoglycemia during the daytime.[5] Thus, 11 of 34 randomly selected, carefully monitored children with insulin-dependent diabetes had episodes of hypoglycemia. It is apparent, therefore, that in short-term studies using intensive monitoring, hypoglycemia is a frequent occurrence in insulin-treated patients with diabetes.

Other investigators have used less sensitive clinical endpoints—that is, the symptoms of hypoglycemia as noted by a patient or the need for medical intervention —to determine the frequency of hypoglycemia over extended periods. Once again hypoglycemia was found to be an important complication of insulin therapy. In one study, hypoglycemia was almost universally observed over a 12-month period in insulin-treated diabetic patients, with only 8% of the patients entirely free from hypoglycemic reactions.[6] Most of the hypoglycemic episodes were minor, but about 17% of the patients had episodes of hypoglycemia severe enough to require glucagon injection.[6] During the one-year

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period of observation about 12% of these patients required admission to hospital for hypoglycemia.[6] In another study, during a one-year period 2 of 15 patients receiving conventional insulin therapy required treatment for hypoglycemia in a hospital emergency room.[7] In a British study, 34% of the patients had at least one severe hypoglycemic episode over a six-month period of observation.[8] Significantly, in this study of 34 patients who had been in a motor vehicle accident, 13 (38%) stated that hypoglycemia was a causal factor.[8] Of course it is possible that these patients attributed their accidents to hypoglycemia when in fact other conditions were primarily responsible. In summary, hypoglycemia is an important and possibly serious clinical problem, as shown in several different insulin-treated diabetic populations.

Not all studies have shown this high a frequency of hypoglycemia. In one study severe hypoglycemia occurred in only 4% of diabetic children and adolescents observed for 18 months.[9] Similarly, in a study in England comparing intensive insulin therapy with the usual insulin regimen, only 2 of 74 patients (3%) required admission to hospital for hypoglycemia during a two-year period of observation (one from each treatment group).[10] Even in these two studies a substantial incidence (1% to 2% per year) of severe hypoglycemia is still reported. The explanation for the wide variation in frequency of hypoglycemia from study to study is not readily obvious. Certain diabetic patients seem clearly at a greater risk for severe hypoglycemia. Additionally, differences in patient education, goals of therapy and therapeutic regimen perhaps explain the different frequencies of severe hypoglycemia. Nevertheless, severe hypoglycemia is not a rare complication of insulin treatment.

Is Hypoglycemia a Serious Side Effect of Diabetic Therapy?

Some clinicians consider an occasional, mild hypoglycemic reaction an acceptable side effect of the treatment of diabetes. There is very little evidence suggesting that mild hypoglycemic reactions that are rapidly relieved by food ingestion result in any long-lasting sequelae. Specifically, to my knowledge there are no convincing data to show that mild hypoglycemic reactions have any long-term effects on cerebral function. As discussed in detail later, however, these hypoglycemic reactions may result in a worsening of diabetic control and for this reason their frequency should be reduced. Even more important, mild hypoglycemic reactions may be the harbinger of severe hypoglycemic reactions, which clearly must be avoided in diabetic patients.

Severe hypoglycemia causes acute neurologic consequences varying from mental dulling to convulsions to coma and death.[11] Treatment with either sugars taken by mouth or glucose given intravenously, which rapidly raises blood glucose levels, usually reverses these acute neurologic complications but, in some instances, recovery does not occur and permanent brain damage results.[11] The frequency of permanent brain damage due to hypoglycemic episodes in diabetic patients has not been carefully investigated. However, various degrees of brain damage due to severe hypoglycemic episodes have unfortunately been observed clinically by most experienced diabetologists, suggesting that it is not a rare event.

An important issue is whether severe hypoglycemic episodes that are apparently reversed with treatment result in any long-term neurologic sequelae. In spite of the great importance of this issue, there has been very little investigation of it. In one study, diabetic patients who had had severe hypoglycemic episodes scored in the abnormal range on a Walton-Black test—which indicates general cortical damage—significantly more frequently than diabetic patients without hypoglycemic episodes.[12] Additionally, in two studies of diabetic children who have had severe hypoglycemic episodes, an increased incidence of abnormal findings on electroencephalograms (EEGs) was reported.[13,14] Diabetic children who had five or more severe hypoglycemic episodes have an increased frequency (80% versus 25%) of abnormal EEGs compared with diabetic children who had not suffered from hypoglycemia. These studies raise the possibility that diabetic patients who have apparently recovered from severe hypoglycemic episodes may have subtle and persistent neurologic sequelae.

The ultimate risk of severe hypoglycemia is death. Many physicians are unaware that hypoglycemia is a significant cause of death in the diabetic population, though several studies from different parts of the world have all shown a substantial mortality due to hypoglycemic events. For example, 2.8% of patients with type I (insulin-dependent) diabetes treated at the Joslin Clinic died due to hypoglycemia.[15] In two other studies, 3.5% of the deaths in diabetic patients younger than age 50 were associated with hypoglycemia,[16] and hypoglycemia was the cause of death in 13% of patients with type I diabetes.[17] In this latter study half of the patients who died of hypoglycemia had undergone hypophysectomy because of proliferative retinopathy. If this high risk group of patients is excluded from the analysis, 7% of the deaths were due to hypoglycemia.[17] In Denmark, 2.8% of deaths in insulin-dependent diabetic patients were due to hypoglycemia.[18] In summary, hypoglycemia is an important and unfortunately common cause of death in insulin-treated diabetic patients. Deaths in diabetic patients thought to be due to other causes may in fact have been precipitated by hypoglycemic episodes. For instance, hypoglycemia could have been the "true" cause of death in a number of instances in which death was attributed to accidents, myocardial infarctions and cerebrovascular insults. Hypoglycemia may be an even more important contributor to mortality than estimated in these studies. Regardless of the precise frequency,

deaths due to hypoglycemia are frequent and represent a tragic complication of insulin therapy.

Does Hypoglycemia Affect Diabetic Control?

Recognition of the importance of hypoglycemia as a cause of unstable diabetes dates back to the 1920s.[19] Since then there have been numerous studies documenting that overtreatment with insulin can result in hypoglycemic episodes followed by rebound hyperglycemia and occasionally even ketosis (the Somogyi effect).[20] Diabetic instability and relative insulin resistance may persist for an extended period (up to 72 to 96 hours) following the hypoglycemic episode. The treatment of this Somogyi syndrome is to eliminate the hypoglycemia by slowly reducing the insulin dosage, which paradoxically results in an improvement in the hyperglycemia.

Both the pathophysiologic basis and the frequency of the Somogyi syndrome in insulin-treated diabetic patients are uncertain. In one study, 90% of unstable diabetic children referred for evaluation were chronically overtreated with insulin based on the presence of symptoms of hypoglycemia and the fact that a reduction in insulin dosage resulted in an improvement in metabolic control.[21] In a clinic population of 300 children, 22 were found to suffer from "brittle diabetes" due to overtreatment with insulin.[22] Overtreatment with insulin and the resulting Somogyi effect may be the basis for poor metabolic control in a significant number of patients with diabetes. Recognition of the hypoglycemic episodes will alert a physician to the possible presence of the Somogyi effect and will result in the proper therapeutic intervention, that is, a reduction in insulin dosage. Other clinical symptoms that suggest overtreatment with insulin include an excessive appetite, weight gain, nocturnal distress, severe nocturnal sweating, extreme variations in glucose levels, frequent ketosis especially in the absence of glycosuria, worsening of symptoms with an increase in insulin dosage and treatment with a relatively high insulin dosage (0.75 to 1.0 units per kg of body weight).[20-22] Any of these symptoms should result in a careful evaluation for hypoglycemia and consideration of a therapeutic trial of a reduction in insulin dosage.

Do Diabetic Patients Have Normal Recovery From Hypoglycemia?

Before discussing whether or not diabetic patients have a complete recovery from hypoglycemia, I will briefly describe the normal physiologic responses to hypoglycemia.[23,24] There are several mechanisms that are potentially important in maintaining blood glucose concentrations. Stimulation of hepatic autonomic nerves can result in an increase in blood glucose levels, indicating a neural mechanism for maintaining glucose homeostasis. Hepatic glucose production is inversely related to plasma glucose concentration, independent of hormonal and neural factors, showing that auto-

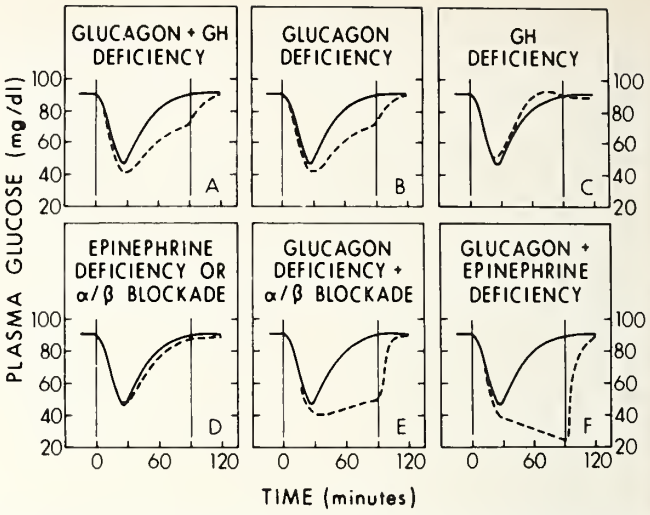

Figure 1.—Plasma glucose curves during insulin-induced hypoglycemia in healthy persons during controlled studies (solid lines) and as modified (dashed lines) by **(A)** somatostatin infusion; **(B)** somatostatin plus growth hormone infusion; **(C)** somatostatin plus glucagon infusion; **(D)** phentolamine plus propranolol infusion or studies in patients who have had bilateral adrenalectomy; **(E)** somatostatin plus phentolamine and propranolol infusion and **(F)** somatostatin infusion in patients who have had bilateral adrenalectomy. (Reproduced with permission from Cryer.[25]) GH = growth hormone

regulation of hepatic glucose production also can be an important mechanism for maintaining blood glucose concentrations. Lastly, hormones (specifically glucagon, epinephrine, growth hormone and cortisol) are secreted abruptly in response to hypoglycemia. Both glucagon and epinephrine increase blood glucose very rapidly (minutes), whereas both growth hormone and cortisol affect glucose homeostasis over a longer time (several hours or days). Thus, the rapid release of growth hormone and cortisol are not important for the immediate recovery from hypoglycemia. Of course, both growth hormone and cortisol are important in long-term glucose homeostasis. Absence of either of these hormones delays the recovery from hypoglycemia and can be associated with severe and often life-threatening hypoglycemia.

If the glucagon response to hypoglycemia is blocked by infusing somatostatin, the glucose recovery is partially impaired and can be returned to normal by glucagon infusion (Figure 1). This shows that glucagon release is an important mechanism in correcting hypoglycemia. If the effect of epinephrine is blocked with adrenergic blockade in healthy persons or in those who are epinephrine deficient (patients who have had both adrenal glands removed and are receiving steroid replacement), the recovery from hypoglycemia is unaffected, suggesting that glucagon alone can elicit the maximal glycemic response and that epinephrine secretion per se is not a crucial factor. When both glucagon and epinephrine are simultaneously blocked, the recovery from hypoglycemia is highly impaired. These

observations indicate that glucagon is the hormone primarily responsible for the recovery from insulin-induced hypoglycemia. When glucagon is deficient, however, epinephrine can compensate for the absence of a glucagon response. If both glucagon and epinephrine are deficient, glucose recovery from hypoglycemia fails to occur. Neuroregulatory and autoregulatory mechanisms are not crucial factors in the recovery from acute hypoglycemia. Thus, the integrity of either glucagon or epinephrine secretion is required for a normal recovery from hypoglycemia.

Patients with insulin-dependent diabetes mellitus commonly have an absent or blunted glucagon response to hypoglycemia.[26,27] The mechanism for this abnormality is unknown, but the absence of glucagon secretion is more common in diabetic patients with autonomic neuropathy.[28] These patients also have a blunted epinephrine response to hypoglycemia.[28-30] As discussed earlier, either glucagon or epinephrine is required for the recovery from acute hypoglycemia. Obviously a diabetic patient with neither a glucagon nor an epinephrine response to hypoglycemia will be at great risk for a severe and long-lasting hypoglycemic reaction.[31]

Reduced glucagon and epinephrine secretions in response to hypoglycemia are acquired features of insulin-dependent diabetes mellitus (Figure 2).[29] Patients studied shortly after the diagnosis of insulin-dependent diabetes mellitus have normal epinephrine and glucagon secretion, those studied after one to five years have reduced glucagon but normal epinephrine responses and those studied after 14-plus years of diabetes have absent glucagon and epinephrine responses. As might be predicted, the recovery from hypoglycemia was normal in patients with recently diagnosed diabetes, somewhat impaired in those who had had diabetes for one to five years and greatly impaired in those who had had diabetes for more than 14 years. Impaired recovery from hypoglycemia is frequent and especially common in those patients with long-standing insulin-dependent diabetes or autonomic neuropathy (or both).

Symptoms and Signs of Hypoglycemia

The symptoms and signs of hypoglycemia can be divided into two general categories—adrenergic and neuroglucopenic.[11,32] The adrenergic symptoms are due primarily to the hypoglycemic-induced release of epinephrine, and the neuroglucopenic symptoms are due to the direct effects of low blood glucose concentrations

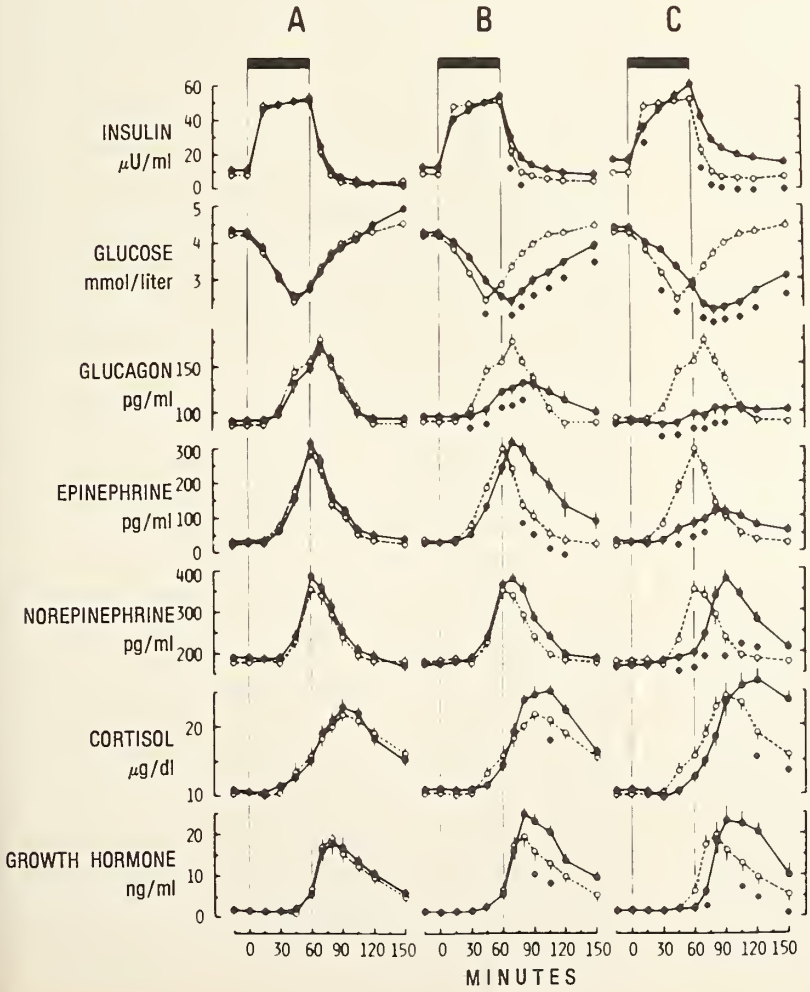

Figure 2—Plasma insulin, glucose and counterregulatory hormone concentrations in response to insulin-induced hypoglycemia in diabetic patients (•—•) and in ten nondiabetic persons (○----○). Insulin was infused from 0 through 60 minutes (28 mU per sq m a minute). Diabetic patients were rendered euglycemic by overnight intravenous infusion of insulin, and the basal insulin infusion rate required to maintain euglycemia from −60 to 0 minutes was continued through 60 minutes (**A,** 5 diabetic patients, diabetes duration less than one month; **B,** 11 diabetic patients, duration one to five years; **C,** 5 diabetic patients, duration 14 to 31 years). $P < .05$, diabetic versus nondiabetic persons. Reproduced with permission from Bolli G, et al.[29])

on glucose-dependent tissues (primarily the central nervous system). The adrenergic symptoms and signs include tremulousness, anxiety, hunger, cold sweats, palpitations and tachycardia. The neuroglucopenic symptoms and signs include headache, weakness, diplopia, confusion, amnesia, bizarre behavioral patterns, uncoordination, seizures and coma.

In addition to the above commonly recognized signs and symptoms of hypoglycemia, a clinician should be aware of other signs and symptoms that can occasionally be due to hypoglycemia. Hypoglycemia can result in hypothermia by both decreasing heat production and increasing heat loss.[11] With severe hypoglycemia, core temperatures can fall below 35°C (95°F). Hypoglycemia may also result in focal neurologic signs, such as hemiparesis.[33] The explanation for these focal lesions is not entirely certain, but it is perhaps due to an underlying structural lesion upon which hypoglycemia is superimposed. Additionally, myocardial ischemia and cardiac arrhythmias can be precipitated or aggravated by hypoglycemic episodes.[34,35]

The signs and symptoms associated with nocturnal hypoglycemia can differ from those described above and are frequently very difficult for both patients and physicians to recognize. The clinical symptoms of nocturnal hypoglycemia include morning headaches, lassitude, night sweats, nightmares, fatigue and difficulty awakening.[4,11] Family members may notice nocturnal distress consisting of pallor, restlessness, stertorous respiration and psychologic changes such as depression, inattentiveness and marital discord.[4,11] Patients are usually not awakened by nocturnal hypoglycemic episodes.[4] Clues to the possible presence of nocturnal hypoglycemia are poor metabolic control, a large daily dose of insulin (greater than 1 unit per kg) and a normal hemoglobin A_{1C} level in patients with known daytime hyperglycemia.[4,36] Only by very close questioning of both the patient and family members can a clinician diagnose nocturnal hypoglycemia.

As discussed in an earlier section, in diabetes with autonomic neuropathy, the epinephrine response to hypoglycemia is frequently impaired. In addition to delaying the recovery from hypoglycemia, the absence of an epinephrine response has another important deleterious effect. Epinephrine is the chief cause of the adrenergic symptoms of hypoglycemia.[37,38] These adrenergic symptoms serve as an "early warning signal" of impending hypoglycemia that, in a properly educated diabetic patient, results in the prompt ingestion of sugar, which will prevent a serious hypoglycemic episode. In a diabetic patient who has decreased or absent epinephrine secretion in response to hypoglycemia, this early warning system is not expressed and only the neuroglucopenic symptoms of hypoglycemia are present. Thus, these patients have an increased potential for severe hypoglycemia. Patients in whom an early adrenergic response to hypoglycemia does not develop should be instructed to recognize the early, subtle neuroglucopenic symptoms of hypoglycemia, such as an inability to think clearly and decreased concentration, so that appropriate therapy can be instituted before more serious neuroglucopenic symptoms develop.

High-dose β-adrenergic blockade with a drug such as propranolol will blunt the recovery from hypoglycemia and also block the adrenergic symptoms associated with hypoglycemia.[39] The increased sweating due to hypoglycemia is an α-adrenergic response and, therefore, this sign of hypoglycemia is preserved in patients treated with β-blockers.[39] Patients treated with β-blockers should, therefore, be instructed in the possible importance and significance of sweating episodes.

Confirming the Diagnosis of Hypoglycemia

The only certain way to diagnose hypoglycemia is to measure the blood glucose level at the time of suspected hypoglycemia. Whereas at one time this was exceedingly difficult to accomplish, with the widespread use of home blood glucose monitoring, it is now possible for diabetic patients to take the necessary glucose measurements at home under their usual living conditions. Blood glucose values of less than 50 mg per dl at the time of a suspected hypoglycemic reaction confirm the diagnosis of hypoglycemia.

Patients will occasionally think they are having a hypoglycemic reaction but their blood glucose levels will not be low. There are several possible explanations for this phenomenon. In normal and diabetic persons decreases in blood glucose concentrations within the physiologic range can activate the adrenergic system,[40,41] which would result in adrenergic symptoms in the presence of normoglycemia. Thus, a patient could experience the typical symptoms of hypoglycemia with a glucose level within the normal range. Another reason for an apparent normal blood glucose level is a delay in taking the blood for glucose measurement. With time, the homeostatic mechanisms described above could raise blood glucose levels into the normal range, resulting in euglycemia in spite of a hypoglycemic episode. For this reason, diabetic patients who measure blood glucose levels at home should be instructed to do a glucose measurement as soon as possible after experiencing a hypoglycemic episode and, certainly, if possible, before ingesting glucose.

Nocturnal hypoglycemia can also be readily diagnosed by home blood glucose measurements. In most cases, if a blood glucose level is done at 3 AM, the diagnosis of nocturnal hypoglycemia will be confirmed.[4] Previously, morning urinary cortisol measurements were thought to be helpful in diagnosing nocturnal hypoglycemia,[42] but this test has not proved to be a reliable indicator of hypoglycemia.[43-45]

How Can Serious Hypoglycemia Be Prevented?

In discussing how to prevent serious hypoglycemia, I will address the following three issues: first, the preventive steps that should be taken in *all* insulin-treated diabetic patients; second, the issues involved in select-

ing patients for aggressive insulin therapy, and, third, the guidelines that are based on my best guess outlining the degree of metabolic control that physicians should aim for in aggressively treating diabetic patients.

General Steps

First and foremost, all patients need to be educated regarding the potential dangers of hypoglycemia. A patient must know the symptoms of hypoglycemia and be instructed in the appropriate response to such symptoms. The importance of always having available a ready source of glucose must be emphasized and the carrying of a Medical Alert Identification bracelet (Medic Alert Foundation International Inc, P.O. Box 1009, Turlock, CA 95380) or other similar identification device is strongly encouraged. Family members and close friends should also be educated so that they know how to recognize and treat hypoglycemia. The effect of food intake, exercise and emotions and the relationship of insulin type and dosage on blood glucose concentrations must be explained to a patient. In patients who have had a serious hypoglycemic episode or who have an increased risk for serious hypoglycemia, family members and close friends should be instructed in the use of glucagon injections to treat such episodes. Measurement at home of blood glucose concentrations should be instituted in patients suspected of having either frequent or severe hypoglycemic episodes.

Selecting Patients for Aggressive Insulin Therapy

In managing diabetic patients, the goals of therapy must be adjusted individually for each patient. The risk of serious hypoglycemia varies greatly from patient to patient, as do the potential benefits of good metabolic control. Obviously, patients who are at the greatest risk for serious and life-threatening hypoglycemic episodes should be less aggressively treated with insulin.

Factors that predispose to serious hypoglycemia and are strong contraindications to aggressive insulin therapy are pituitary insufficiency, adrenal insufficiency, end-stage liver or kidney disease, autonomic insufficiency, ethanol abuse, psychiatric disturbance and the use of high dosages of β-blocking agents, such as propranolol. An additional strong contraindication to aggressive insulin therapy is the inability of a patient to measure blood glucose levels at home or to be educated sufficiently to undertake the responsibility for extensive self-care.

Two recent studies have used the response to insulin-induced hypoglycemia, in a carefully controlled clinical environment, as a test to determine which patients are at an increased risk for serious hypoglycemic reaction. In one study,[46] a delayed or absent rise in the glucose level after hypoglycemia predicted an increased risk of serious hypoglycemia with aggressive insulin therapy. However, the other study[47] of somewhat different design failed to identify a correlation of serious hypoglycemic episodes and abnormalities of glucose homeostasis during insulin tolerance testing. Thus, until further studies are done, the routine use of insulin tolerance testing to detect patients with an increased susceptibility to serious hypoglycemic episodes cannot yet be recommended.

In some patients the potential complications associated with hypoglycemia are more serious and in this group of patients, aggressive therapy should not be undertaken lightly. For instance, in patients who have cerebrovascular or coronary artery disease, the consequences of hypoglycemia may be exaggerated in hypoperfused tissues. Similarly, patients who live alone or wherein the socioeconomic situation is not ideal are more likely to suffer serious consequences from a hypoglycemic episode.

The goal of tight metabolic control is to try to prevent microvascular complications of diabetes. If there is already severe microvascular disease, tight metabolic control does not affect the course of either the diabetic retinopathy or nephropathy.[7,48,49] Therefore, if a patient already suffers from end-stage microvascular disease, institution of a regimen of tight metabolic control is usually not indicated. Similarly, the microvascular complications of diabetes usually take between 10 and 20 years to develop[50,51] and, therefore, if a patient's life expectancy is greatly reduced due to other medical conditions, aggressive attempts to control glucose levels are also not usually indicated. It is very important for a physician to tailor a therapy regimen to the individual needs of each patient. Standardized therapeutic regimens and goals have no place in the management of diabetic patients.

Goals of Glycemic Therapy

Despite clinical impressions and a large number of suggestive results from experiments using animals, absolute *proof* that good metabolic control will prevent the microvascular complications of diabetes is not yet available. In selected patients, though, the goal of therapy should be to reduce blood glucose levels to normal limits. In a patient who is capable of understanding his or her diabetes, is healthy and has no contraindications to aggressive metabolic therapy, attempts to tightly control glucose levels should be instituted. The glycemic control that I aim for is to maintain fasting plasma glucose concentrations between 100 and 140 mg per dl and two-hour postprandial plasma levels between 100 and 200 mg per dl. I base my choice of these values on prospective studies both in England and in Pima Indians showing that the incidence of microvascular disease in persons with fasting plasma glucose levels of less than 140 mg per dl and two-hour postglucose ingestion values of less than 200 mg per dl is very low.[51,52] It seems to me, therefore, that plasma glucose values in this range should be able to minimize microvascular disease and that the risk of hypoglycemia is considerably less than if one attempts

to more stringently control glucose levels. Similar glycemic goals have been proposed by others.[53]

Patients who attempt to control glucose levels within this range must measure their blood glucose levels frequently at home, including occasionally at 3 AM. Adjustments in therapy must be based on frequent home blood glucose measurements. Frequent or severe hypoglycemic episodes must result in adjustments in therapy (changes in insulin dose, diet, exercise and the like) and should not be accepted as a benign side effect of therapy. Frequent or severe hypoglycemic episodes must be avoided even if this results in not meeting the goals of glycemic control cited earlier. Both physicians and patients must recognize that with conventional insulin therapy the goals cited above may not always be achievable despite diligent efforts by both.

Discussion

DR MARVIN SIPERSTEIN: Perhaps I am biased, but I think that Dr Feingold has presented an excellent, very balanced discussion of a practical subject that diabetologists, in particular, would like to forget about. If we saw 3% to 5% deaths with drugs such as penicillin or levothyroxine, we would at least pause before using these drugs unless their efficacy had been overwhelmingly proved. One might accept 3% to 5% deaths from hypoglycemia if it had been shown conclusively that insulin really prevented microangiopathy or macroangiopathy, but over the past year increasing evidence indicates that insulin not only does not prevent microangiopathy but that very tight control may actually accelerate microangiopathy. There are several studies showing this lack of efficacy.[7,10,47,48,54,55] This has given us even more reason to question whether in 1983 very tight control is justified, given the sort of mortality and morbidity from hypoglycemia described today.

DR PETER FORSHAM: My main comment is that very tight control is indeed a dangerous thing and should not be used in people who have had diabetes for more than 30 years. I cannot agree with Dr Siperstein, however, that there is no evidence that insulin is useful in preventing the complications of diabetes. The evidence is overwhelming and these papers that show too much insulin promotes small vessel disease describe only a few cases. When you look at the field of diabetes treatment as a whole, there is no question that insulin, at least over the past 50 years, has proved lifesaving. Anything that proves lifesaving also has hidden dangers. These dangers were brought out beautifully in this conference, which shows that insulin has to be used with care.

As for the level of glycemic control, I agree with Dr Feingold that blood glucose levels of 100 to 200 mg per dl postprandially are perfect. In actual fact, most diabetic patients under tight control have blood glucose values in that range. The only exception is in pregnant diabetic patients, whose blood glucose levels are now maintained at between 70 and 130 mg per dl on incomplete evidence that a value as high as 150 mg per dl is bad.

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Epitomes

Important Advances in Clinical Medicine

Nuclear Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in nuclear medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

The Role of Nuclear and Ultrasonic Thyroid Imaging

THE MANAGEMENT of thyroid nodules is troublesome because of the low but significant incidence of thyroid cancer in them and because there is not always a clear advantage in the risk of a definitive diagnosis by means of a surgical procedure versus the risk of overlooking a malignancy. An unnecessary operation can be obviated by using nonsurgical diagnostic procedures to identify those cases wherein the likelihood of malignancy is low. Noninvasive radionuclide scintigraphy and ultrasonography are almost universally available and can aid in such differentiation.

Thyroid scintigraphy identifies the 20% to 25% of thyroid nodules that are of equal or greater function than adjacent healthy thyroid. These nodules have such a low incidence of malignancy that a surgical procedure is not indicated. A solitary inactive nodule has a 10% to 30% chance of being malignant. A palpable nodule and scan must be correlated at the time of scanning to detect the nodule and accurately identify its activity. Sodium iodide I 123 and sodium pertechnetate Tc 99m are presently the radionuclides of choice.

Diagnostic ultrasound identifies the 10% to 15% of nodules that are purely cystic. These are rarely malignant. High-resolution real-time ultrasound has a greater ability to differentiate purely cystic from mixed but predominantly cystic nodules.

Because a radionuclide study has the potential to identify a larger population that does not need surgical intervention, it should be the imaging procedure of choice unless there is a contraindication to the small amount of radiation exposure. The remaining population (those with cold nodules) can be further evaluated by the use of ultrasound, thereby reducing the need for invasive procedures—that is, needle biopsy or surgical procedure or both—by 25% to 35%.

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Assessment of Liver Lesions Using Single-Photon Emission Computed Tomography

CONVENTIONAL LIVER SCINTIGRAPHY has been used extensively for the evaluation of focal and diffuse hepatic disease. The procedure is safe, accurate, very reproducible and widely available; overall accuracy for focal liver disease is about 80% in most published series. The technique is somewhat limited, however, by the relative lack of resolution of most defects less than 2 cm in diameter, especially deeper within the liver. Computed tomography (CT) and ultrasound typically can resolve 1-cm hepatic lesions and are most accurate nearer the center of the liver where conventional nuclear imaging is least sensitive.

Single-photon emission CT is a new technique available for liver imaging. The method requires a special γ-camera with a yoke configuration that allows the

camera crystal to rotate around a patient and collect data from either a 180 degree or a 360 degree angle. A computer collects and stores the data, and images are formatted into transverse sections in a manner analogous to transmission CT. The conventional radiopharmaceuticals, such as technetium Tc 99m sulfur colloid, are used; however, the potential for imaging in a transaxial tomographic format with other tracers such as blood flow agents or tumor-specific antibodies is being actively investigated.

It is claimed that single-photon emission CT is 92% accurate in detecting focal liver lesions compared with 82% for conventional planar imaging. It is possible that this technique will detect over half the lesions between 1 and 2 cm in diameter, which conventional scintigrams rarely detect. Studies in Sweden by Lassen and co-workers suggest that its accuracy should be comparable to transmission CT, yet it should be a less expensive procedure and one in which injection of contrast material is not necessary.

Present limitations of single-photon emission CT in the liver include possible artifacts created by imperfect camera motion or computer algorithm. Interpretation of liver images produced by this method requires a working knowledge of cross-sectional anatomy and care must be expressed to avoid misinterpreting a normal portal or fissural structure as a pathologic lesion.

Single-photon emission CT will significantly add to the accuracy of nuclear liver imaging, and many lesions that might have been missed will be clearly seen.

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Radionuclide Determination of Brain Death

THE DECISION to discontinue life-support measures in a patient suspected of having brain death demands utmost certainty and is one laden with moral, legal and financial considerations.

A brain death diagnosis is first suspected by findings on physical examination and further supported, or not supported, by results of (often serial) electroencephalography. There still may be uncertainty. Additional confirmation is often needed or desired, particularly when hypothermia or extreme sedation is present, or when the patient is a child.

Radionuclide cerebral blood flow studies are highly specific and quite sensitive in diagnosing brain death. The pathophysiology is the same as in cases of absent cerebral blood flow by contrast angiography in which intracranial pressure (due to ischemic cerebral edema) exceeds intracranial systolic blood pressure resolution.

In our experience (107 patients), specificity is very high (all who lived had negative studies) as is sensitivity (up to 85%), depending on the time of scan in relationship to actual brain death. In the literature and in our experience there are no reports of survival in patients with absent cerebral blood flow (positive predictive value of 100%). The study can easily be done at the bedside with a mobile camera using a bolus intravenous injection of technetium 99m. It is a highly reliable aid in the evaluation of brain death.

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Schwartz JA, Baxter J, Brill D, et al: Radionuclide cerebral imaging confirming brain death. JAMA 1983 Jan 14; 249:246-247

Radionuclide Detection of Acute Lower Gastrointestinal Tract Bleeding Site

IDENTIFYING AND LOCATING active lower gastrointestinal tract hemorrhage is a serious clinical problem, particularly when surgical intervention is necessary. In many institutions, radionuclide imaging studies have become firmly established as the principal method for locating the bleeding site. These rapid and noninvasive scintigraphic techniques have largely supplanted angiography because they have proved nearly twice as sensitive for detecting bleeding sites. Bleeding sites in patients with intermittent bleeding and in those with bleeding rates below 0.5 ml per minute often cannot be detected by angiography. When the study does detect a bleeding site, contrast angiography can be directed to evaluate a specific region of the gastrointestinal tract.

The nuclear imaging studies involve intravenous administration of a radiopharmaceutical agent that remains in the circulation long enough to allow scintigraphic visualization of extravasation at the site of active bleeding.

The technique involves labeling a patient's own erythrocytes with technetium 99m by a simple and rapid modification of the standard in vivo method commonly used for gated cardiac scintigraphy. The long retention time of labeled erythrocytes in the circulation allows prolonged sequential scintillation camera imaging, which can accurately diagnose the site of hemorrhage even in intermittent bleeders. Computer acquisition of sequential one-minute images during the first 60 to 90 minutes after administration of the labeled cells allows playback in a movie format that enhances localization. These dynamic displays show that extravasation is commonly intermittent even in patients who have massive acute hemorrhage.

If no bleeding site is found within 90 minutes, hourly images for up to 24 hours may be helpful to identify intermittent bleeding. In patients with positive delayed views, a new series of sequential images may sometimes show continued extravasation at the true bleeding focus.

The ^{99m}Tc erythrocyte study is safe and has no contraindications. The radiation dose is small, particularly when compared with that for angiography. It has high

patient acceptability and can be done at the bedside with a mobile scintillation camera when a patient is too ill to move. It is the study of choice in patients requiring transfusion for acute hematochezia or melena when the site of hemorrhage is not clinically obvious.

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Nuclear Magnetic Resonance Imaging

CLINICAL TRIALS carried out over the past three years have validated the clinical use of nuclear magnetic resonance (NMR) imaging. Some of the advantages of NMR over existing imaging modalities include intrinsically high soft tissue contrast resolution, the ability to image in any plane with equivalent spatial resolution in all planes and the capability to delineate flowing blood without contrast material. It is entirely noninvasive, uses no ionizing radiation and has shown no adverse biologic effect. The typical initial cost of a nuclear magnetic resonance unit is between $800,000 and $1.5 million (excluding installation), compared with $600,000 to $1 million for a computed tomography (CT) system.

Clinical NMR systems produce images dependent on the magnetic properties of the hydrogen nucleus (proton). A patient is placed in a strong magnetic field and exposed to low energy (radio frequency) radiation, some of which is absorbed by protons aligned in the magnetic field. As the protons subsequently release the energy absorbed, the signal produced is detected as induced electrical currents in a receiver coil, which are processed by computer and displayed as transaxial, coronal or sagittal images.

Nuclear magnetic resonance imaging of the central nervous system has received considerable attention. There is very little NMR signal from the skull, allowing the surface of the adjacent brain to be clearly seen. This is particularly useful for imaging the posterior fossa where CT signals from the bone may cause artifactual image streaking. Brain scans using this technique show superior soft tissue contrast to that of CT and have been used to identify early lesions of multiple sclerosis in patients with normal findings on CT scans.

Nuclear magnetic resonance has also proved useful in diagnosing cardiovascular disease. Blood flowing at normal velocities generates little or no NMR signal. This results in a high natural contrast between the lumen and the walls of blood vessels, without the use of intravenous contrast agents. Thus NMR imaging is useful in defining vascular pathology and, in particular, atherosclerotic lesions. Using cardiac gating techniques, excellent images of the heart have been produced allowing visualization of congenital defects, mural thrombi and valvular disease. It appears that NMR cardiac imaging will have great value as a noninvasive means of detecting, locating and quantifying myocardial infarcts.

In the mediastinum, nuclear magnetic resonance has an advantage over CT in clearly distinguishing between blood vessels and masses.

Abdominal NMR images have excellent soft tissue resolution and clearly show the major intra-abdominal, retroperitoneal and pelvic organs. NMR images of the abdomen (without contrast administration) are comparable with contrast-enhanced CT images, but the precise role of abdominal NMR imaging vis-à-vis CT scanning remains to be further investigated.

Nuclear magnetic resonance images contain information that is fundamentally different from the anatomic images from CT and ultrasound, and may form a basis for visualizing chemical and physiologic processes at the cellular level. Exploring this potential to detect and monitor the metabolic and pathophysiologic features of tissues in vivo is the current challenge to NMR research.

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Noninvasive Evaluation of Obstructive Versus Nonobstructive Uropathy

THE DIFFERENTIAL DIAGNOSIS of hydronephrosis includes complete or partial obstruction to the transit of urine from the renal pelvis to the bladder, the sequelae of an old obstructive uropathy that has resolved and back pressure atrophy from vesicoureteral reflux, as well as various other inflammatory, neurogenic and congenital conditions. An acute obstruction can generally be diagnosed by doing a standard urogram using contrast material administered intravenously. A partial obstruction will eventually compromise renal function and yet may be resolved with appropriate surgical intervention. The "gold standard" for diagnosing a partial obstruction is the Whitaker test. Unfortunately, this is a fairly invasive test because it involves a percutaneous nephrostomy and placement of a Foley catheter in the bladder.

A noninvasive alternative to the Whitaker test is the furosemide (Lasix) renogram. This study is done simply as an adjunct to a standard technetium 99m-labeled DTPA (pentetic acid) radionuclide renal scan. Furosemide (0.05 to 1.0 mg per kg of body weight) is administered intravenously ten minutes after administration of DTPA. Data are accumulated on a computer for 25 to 30 minutes. Activity in the region of interest, chosen to include the kidney and its dilated collecting

system, is then recorded by computer-generated curves as a function of time. If the collecting system is dilated but not obstructed, at least 50% of the activity will wash out from the collecting system by 15 minutes after intravenous administration of the furosemide. This study is relatively noninvasive and provides results that correlate well with those of the Whitaker test.

If enough renal parenchymal disease is present to limit the ability of the kidney to increase its urine flow in response to diuretics, the furosemide renogram could be falsely positive for partial obstruction and this constitutes the major limitation of the technique. In the presence of dilated collecting system(s), by expanding the study to a furosemide renogram it will be possible to differentiate obstructive from nonobstructive uropathy. In most cases this will obviate the need for a confirmatory Whitaker test.

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Indium 111-Labeled Leukocyte Scanning

LEUKOCYTE SCANNING using indium 111 is now established as a valuable technique for detecting acute inflammatory processes. Accurate identification and noninvasive localization of abdominal and occult abscesses are the primary indications for doing this study. It has been proved conclusively that the ^{111}In-labeled leukocytes retain their viability and function while concentrating avidly in areas of abscess and inflammation. The labeling technique is simple and efficient and can be incorporated into most nuclear medicine departments. Both autologous and heterologous cells have been used successfully. The radiolabeled leukocytes are not excreted through the bowel or kidneys, which offers a significant advantage over gallium 67 scanning. The study is generally completed within 24 hours, and large series consistently report sensitivities, specificities and accuracies greater than 90%. The ^{111}In-labeled leukocyte scan is most valuable in a patient suspected of harboring an abscess or an acute inflammatory process without focal signs or symptoms. A negative result is strong evidence against the presence of a significant inflammatory process, while a positive result can expedite diagnosis and therapy.

The areas of greatest clinical use thus far include suspected abdominal abscesses without focal signs to indicate their location, postoperative patients, occult abscesses outside the abdomen, inflammatory bowel disease and bowel infarction. Conditions in which the leukocyte scan has proved to be less useful include pyelonephritis, bone and joint disorders (with the possible exception of acute osteomyelitis), bacterial endocarditis and fungal, parasitic and chronic infections. Success with ^{111}In-labeled leukocytes has stimulated research to evaluate their possible use in interstitial lung disease, rheumatic diseases and vascular infections.

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Hepatobiliary Scintigraphy in the Diagnosis of Acute Cholecystitis

WITHIN THE past few years a new class of technetium 99m-labeled radiopharmaceuticals has evolved and revolutionized the diagnostic examination of patients who may have acute cholecystitis. Loosely referred to as "HIDA" (the US Pharmacopeial Convention code designation for lidofenin), these compounds have become the standard for hepatobiliary imaging. Of the HIDA compounds, diethyl-iminodiacetic (IDA) and diisopropyl-IDA have been found most satisfactory because of their comparatively better pharmacokinetics and decreased fractional renal excretion.

Patients appropriately selected for HIDA scans are those suspected of having acute cholecystitis because of typical signs and symptoms of the disorder, including right upper quadrant abdominal pain, fever, leukocytosis and so forth. After a negative history of cholecystectomy is obtained and the patient has fasted for two hours, HIDA is injected and images taken serially with a scintillation camera for up to two hours if necessary. A normal gallbladder will appear 30 minutes to an hour later. If the gallbladder does not appear, cystic duct obstruction and associated cholecystitis are inferred. From reported series (including more than 1,000 patients) the sensitivity and specificity in this study exceed 95% even with serum total bilirubin levels of up to 4 mg per dl.

Certain cautions are advisable in inferring cholecystitis from HIDA scans. A loss in specificity, which may be considerable, can occur under some circumstances. For instance, the test has been found to be undependable in poorly nourished patients, especially in those who have alcoholism, those persons subjected to fasting of more than one day's duration (such as patients receiving long-term intravenous hyperalimentation) and in patients with total serum bilirubin levels of greater than 4 mg per dl.

A comparison between ultrasonography and HIDA scans in diagnosing acute cholecystitis has led to animated discussions, but with the above cautions, a substantial majority of experts agree that HIDA scans are superior to ultrasonography in spite of an approximate 20% cost savings of the latter. This is because ultrasonographic characteristics of acute cholecystitis are nonspecific—that is, not all patients with gallstones have acute cholecystitis; also, the cystic duct may be blocked without stones identified in the gallbladder by ultrasonography. Additionally, ultrasound studies can-

not be technically interpreted in some cases (for instance, gallbladder not identified, overlying gas or dressing precludes ultrasonography). In conclusion, HIDA scans can be recommended as the single test of choice in objectively documenting the presence of acute cholecystitis.

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Thallium 201 Myocardial Imaging in the Diagnosis of Coronary Artery Disease

THALLIUM 201 stress scintigraphy has now been widely accepted as an important clinical tool that substantially improves the accuracy in diagnosing noninvasively the presence, extent and severity of coronary artery disease. The ^{201}Tl tracer is administered during peak exercise. The immediate post-stress images reflect regional myocardial blood flow, whereas the delayed images—that is, recorded four hours later—reflect myocardial viability. A transient defect (one that resolves from the early to the late images) represents stress-induced ischemia, whereas a persistent defect usually represents myocardial scars. Because the ^{201}Tl distribution in myocardium reflects the pathophysiologic consequences of coronary stenosis on myocardial blood flow rather than on the coronary anatomy, the test provides functional information that is not available through routine coronary arteriography. Compared with electrocardiography (ECG), images obtained with the use of ^{201}Tl yield accurate information on location, extent and number of myocardial segments affected by ischemia as well as the presence of necrotic or scar tissue, information that is of considerable prognostic value in patients with ischemic heart disease.

The sensitivity (80%) and specificity (91%) of ^{201}Tl stress testing for detecting coronary artery disease are considerably higher than those of electrocardiographic stress testing (60% and 81%, respectively). An important consideration for the clinical use of ^{201}Tl stress scintigraphy is that the probability of coronary artery disease developing in a given person after the test largely depends on the pretest probability as determined by age, sex, symptoms and risk factors. Thallium 201 stress testing affects the probability of disease only little in patients with a high pretest probability. Routine diagnostic use of the test therefore does not appear justified in this particular patient population. By contrast, the test considerably alters the probability of coronary artery disease in patients with a moderate pretest probability. Accordingly, the exercise ^{201}Tl scan is clinically indicated in patients who have (1) typical chest pain but no resting or stress ECG abnormalities, (2) abnormal findings on stress ECG but no symptoms, (3) atypical chest pain and equivocal results of stress ECG and (4) known ischemic heart disease considered for surgical treatment in order to gain additional prognostic information before and after operation, and to assess the physiologic significance of a questionable coronary artery lesion seen on angiography. Other indications for ^{201}Tl stress scintigraphy are exercise-induced chest pain but normal or minimal lesions of coronary arteries. In these patients, an inappropriate vasoconstriction (coronary vasospasm) elicited by exercise may be responsible for the anginal symptoms. Thallium 201 may then be a useful tool for clarifying the underlying pathogenetic mechanism of ischemia.

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Detection of Skeletal Metastasis—A Rational Approach to the Use of Nuclear Bone Imaging and Radiography

SINCE THE ADVENT of technetium Tc 99m phosphate bone-seeking radiopharmaceuticals, the relative efficacy of scintigraphic bone scanning and x-ray skeletal survey has been extensively investigated. There is substantial agreement about the results and the clinical implications of several published studies, and it is important for practicing physicians to be aware of these findings so that they may apply them more efficiently and economically in practice.

Nuclear bone scanning is significantly more sensitive than x-ray studies in detecting metastatic bone lesions. In considering metastatic lesions of all origins, the nuclear scan will detect about 80% more lesions than radiography, whereas only about 2% of lesions seen radiographically will not be detected on the nuclear study. Most of the cases missed by nuclear bone scanning are due to specific conditions. Given the clearly superior sensitivity of nuclear bone scanning compared with radiology in the detection of metastasis, together with the fact that this procedure is less laborious and involves less radiation to patients, it is, in most instances, the method of choice in the screening of patients for metastatic bone disease. It has been shown that areas that are positive on bone scan frequently take from 6 to 18 months to be noted radiologically.

While a nuclear study is extremely sensitive, positive findings are often not specific enough to make a diagnosis of metastatic disease with certainty. It is there-

fore most important that x-ray films be taken of scintigraphically positive areas to rule out benign disease. Multiple scattered areas of scintigraphic abnormalities in the absence of abnormal x-ray findings usually imply the presence of metastatic disease. However, given the presence of a primary malignant lesion, a single area of abnormality on bone scan correlates with metastatic involvement in about 50% of cases and, if that area happens to be a rib, in only 20% to 24% of cases. Thus, in patients with a single abnormality noted on scanning or in patients who have multiple abnormalities and normal findings on x-ray, "coned-down" views or computed tomography of limited areas may more clearly define the nature of the lesion(s). Bone biopsy may be indicated if results of tomography are not diagnostic and the definitive answer to that question will affect the immediate treatment plan. Otherwise, follow-up studies usually provide the information needed.

The most likely metastatic lesions to be missed on bone scans are due to multiple myeloma, thyroid carcinoma and some rapidly progressing lesions that are purely lytic on x-ray study.

In general, roentgenography is more helpful in following known metastatic lesions for response to therapy. Bone scintigraphy, on the other hand, may show increase in uptake of the radiopharmaceutical agent in a previously identified lesion because of healing or deterioration.

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Editorials

Pressures and Pressure Vacuums

IT IS NO NEWS that changes are occurring in the practice of medicine and in the delivery of care to patients —changes being driven by the economic impact of rising costs. This state of affairs has been brought about by the enormous success of the national effort over several decades to develop medical science and to bring the resulting improvements to as many people as possible. And now the payors, especially industry, labor and government, who in one way or another foot most of the health care bill, have revolted over the issues of the rising costs. They are demanding and mandating that new forms of medical practice and patient care be tried. The approach being used is to pit physicians against physicians, hospitals against hospitals and pressure groups against pressure groups in the hope that the resulting "competition" will bring about a healthy reduction in the cost of health care.

Curiously, those most directly affected have had relatively little to say about what is being done. Physicians are only a minority in the health care enterprise and organized medicine is all too often viewed as a pressure group interested in promoting its own self interest. Little attention is being paid to what might be called the *nuclear unit* in most of health care. This comprises a physician, a patient and the action that takes place between them as they collaborate to bring the science and art of medicine to bear in treating illness, injury or emotional disturbance. In the process they of course engender many if not most of the costs of health care. Traditionally organized medicine has tried to act as representative for this nuclear unit and has developed some considerable skills and effectiveness in protecting and enhancing the quality of the care rendered in it. But the new economic pressures are something else. Too often the medical profession and what are called the consumers of health care (patients) are now being passed over and not even consulted about decisions affecting them and the health care they will be giving and receiving.

Clearly there is a pressure vacuum, or at least a partial pressure vacuum here. In the pitting of pressure group against pressure group, the pressures generated in behalf of the nuclear units of health care are proving less than a match for the pressures being generated by industry, labor and government in their efforts to reduce costs. Hence the providers and consumers of health care are now finding themselves in positions of relative weakness.

But need this be so? Physicians and the medical profession enjoy a substantial amount of public trust and approval as attested in almost every poll of public opinion on the subject. Patients and their relatives and friends permeate the fabric of society in substantial numbers, and hundreds of thousands of contacts occur each day in the ordinary course of events in the nuclear units of health care. Is not this the stuff for a powerful pressure group? We are pleased to note that the California Medical Association has begun to develop this potential source of strength for better health care, and we urge other medical associations to consider using this approach, which everywhere could become a powerful force to influence local and state as well as national issues in health care.

MSMW

The Cytotoxic Test

IN 1956 BLACK[1] DEVISED an in vitro test for food allergy based on the prior claim of Vaughan[2] and others that ingestion of a food produces leukopenia in a person allergic to that food. Black's test was later popularized by Bryan and Bryan,[3] and it has come to be known as the cytotoxic test for food allergy.

The test is carried out by placing a drop of the patient's leukocyte buffy coat suspended in a mixture of plasma and water onto a siliconized microscope slide coated with a dried extract of the food to be tested. The unstained preparation is examined microscopically for a period of up to two hours for observable changes in leukocyte morphology. A positive result is recorded if rounding, inactivity, vacuolization and disintegration of cells are observed.

Several reports in the medical literature claim that the test is useful in the diagnosis of food allergy, although none of these claims satisfy the usual criteria for controlled trials.[4] Properly controlled studies, on the other hand, have uniformly failed to show a correlation between the results of the test and the presence or absence of clinical reactions to these foods when they are eaten.[5,6] The fact that controlled studies do not substantiate the claims of proponents of the test is not surprising in the light of current knowledge of the pathogenesis of allergic diseases. Immunological cytotoxicity can occur through antibody-dependent, complement-dependent and lymphocyte-mediated mechanisms. These are believed to be important in immunity to infectious agents and neoplasms, but they have yet to be implicated in any known manifestations of food intolerance.

The techniques required to show immunologically induced cytotoxic and cytolytic reactions are far more fastidious than those used in Bryan's cytotoxic test.[7] Changes in cell morphology using Bryan's method could be produced by extraneous factors, such as pH, osmotic pressure, temperature, contaminants in the food extract and time of incubation. None of these variables has been standardized or adequately investigated for an effect on the test results. Furthermore,

the nature of the procedure precludes identification of specific cell types under observation.

Nevertheless, the use of cytotoxic tests is becoming increasingly more popular, and is promoted in nonprofessional books and magazines,[8] particularly those that encourage self-help in matters of health and well-being. Newspaper advertisements throughout California appear regularly from laboratories offering this test directly to the public without the requirement that patients be seen by a physician. One such advertisement in a gay newspaper implied that the cytotoxic test for food allergy can be used in the diagnosis of acquired immune deficiency syndrome (AIDS).

In California an unlicensed laboratory can offer the test directly to the public because of a determination by the Laboratory Field Services division of the Department of Health Services that "information derived from cytotoxic testing is not used to diagnose 'disease in human beings' " (as defined by the Business and Professions Code) "but rather is being used to provide dietary counseling" (R. D. Hamblin, written communication, April 1982).

This ruling is a clear denial of the obvious facts. The originator and proponents of the test devised it for the specific purpose of establishing the diagnosis of food allergy. The test is usually offered for the determination of "allergy" to 150 or more foods at a cost to the patient of $300 to $500. The patient receives a copy of the "results" and an explanation stating (1) that this is a "test," (2) that a positive result indicates that certain foods are toxic to the patient's leukocytes and (3) that the patient is therefore allergic to that food.

The problem of allergy to foods is a controversial one that divides allergists and confuses physicians and patients alike. Anaphylactic reactions to foods, especially seafoods, legumes, nuts and berries, are well recognized, easily diagnosed and fortunately rare. Delayed gastrointestinal reactions to foods are more common and probably encompass both allergic and nonallergic causes. The association of other adverse effects with foods, particularly behavioral and cognitive changes and poorly defined symptoms such as fatigue, are in most cases spurious, as shown by double-blind challenge studies of May[9] and others. Certain foods contain pharmacologically active chemicals, occurring either naturally or by contamination or deliberate addition, and these may be responsible for adverse effects in some patients. A thorough clinical history is essential in the evaluation of each case.

A practitioner who is confronted by a difficult diagnostic problem may be tempted to order a cytotoxic test. Before doing so, the physician must be aware that the test procedure—while appearing to be a diagnostic test—has no rational basis or proved ability to detect allergy or to determine the nutritive value of foods. An elimination diet based on a faulty test is not in a patient's best interest and can reinforce the belief in a nonexistent food allergy in addition to risking the development of nutritional difficulties.

California's Department of Health Services is wrong in its interpretation of the cytotoxic test. The test cannot offer information useful in dietary counseling, and it cannot be used to diagnose allergy. Nevertheless it is *in fact* being used for this purpose, and laboratories offering the test are diagnosing disease and therefore engaging in the practice of medicine. Permitting unlicensed laboratories to carry out a worthless and misleading procedure is a clear abrogation of the role of government in protecting the public's health through its regulation of health facilities.

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Prolactinoma

In this issue Dr Martin and colleagues have reviewed their experiences and impressions regarding the epidemiology, presentation, diagnosis and treatment of prolactinoma—the most common hypothalamic-pituitary disease seen in clinical practice.[1] Why is the disease so common and has its incidence changed? We have no evidence that the disease is occurring any more frequently now than previously. The diagnosis was clearly missed before prolactin was recognized in 1971 as a hormone separate and distinct from the growth hormone in humans. With the advent of specific and sensitive radioimmunoassays for prolactin, hyperprolactinemia was demonstrated to be a common condition that accounted for not only 15% to 30% of cases of amenorrhea in gynecologic practice, but also for 50% to 60% of cases of the hitherto most common pituitary tumor—the "nonfunctioning" tumor.[2]

All endocrine tissues have a propensity for adenoma formation and the pituitary is no exception. The study by Costello indicates that this is certainly true.[3] As it was carried out in the 1930s, this study did not address whether those tumors were prolactinomas. More recently, however, Burrow and co-workers evaluated postmortem radiographic and macroscopic and microscopic findings in the pituitary and showed there was a significant incidence (11%) of prolactinoma in both men and women at all ages.[4] Furthermore, they provided data that questioned the specificity of tomography in identifying changes of the sella turcica associ-

ated with microadenomas. What, then, is the optimum neuroradiological approach for examination of the pituitary in 1983? Most investigators agree that neither plain skull x-ray films nor tomography is helpful in diagnosing microadenomas or, for that matter, macroadenomas. These radiological techniques examine the bony tissues rather than the soft tissues of the pituitary. The high-resolution computed tomography (CT) scan best defines the pituitary anatomy (including soft tissue) and allows diagnosis of macroadenomas and some microadenomas, as well as identification of suprasellar extension or empty sella syndrome. Indeed, the need for pneumoencephalography for pituitary disease is now almost entirely eliminated.

Who should be screened for the presence of a prolactinoma and are there any pathognomonic signs of the condition? The incidence and presentation of a prolactin-secreting adenoma are different in men and women, although the pathological studies would suggest the prevalence of prolactinomas is similar in the two sexes.[4] The condition is more frequently diagnosed in women who present with menstrual problems or infertility. Although women often have galactorrhea, some do not, even on careful examination. Because about 50% of women with galactorrhea have normal serum prolactin levels, the presence of galactorrhea is a poor discriminator of the presence or absence of hyperprolactinemia. Examination of the large surgical series of 330 patients reported by Hardy shows that 68% of the women had microadenomas, while 83% of the men had macroadenomas.[5] Thus the men present late in the course of their disease with symptoms resulting from expansion of their tumor, such as visual field defects and headaches. They too are hypogonadal but are often unaware of this until following treatment they realize all they have been missing!

The major controversy in this subject relates to the optimal management of these patients. At the outset it has to be stated that there are certain unknowns which make it impossible to give a definitive answer. Such questions include the following: (1) What is the natural history of a prolactinoma? (2) What are the surgical results? (3) How often is recurrence seen after a "successful" surgical procedure? (4) Does medical therapy affect the natural history of the disease? The answers to each question are long, circuitous and unsatisfactory. It is likely that in most instances these tumors run a very benign course and probably do not progress; occasional tumors, however, are aggressive and the question is how to distinguish them prospectively; at present there is no answer.

The surgical results vary. The perspective given in Dr Martin's paper is biased because the University of California, San Francisco (UCSF), is a major national referral center for pituitary microsurgery and their results are not representative of neurosurgical removal of microadenomas in an average hospital. Even in the major centers such as UCSF, where operations are carried out every day by highly skilled neurosurgeons specializing in transsphenoidal pituitary microsurgery, the results are only satisfactory when the pretreatment serum prolactin value is less than 200 ng per ml. Moreover, a definite incidence of recurrence of hyperprolactinemia months or years later is now being recognized[6] and, therefore, the simplistic view of the operation as a lifelong cure has to be questioned.

What about medical therapy? Medical therapy with dopamine-agonist drugs, of which bromocriptine is the prototype, is well established and experience now spans 13 years in Europe. Bromocriptine has been approved for limited application in the United States. The drug, acting as a functional analogue of dopamine, the physiological prolactin-inhibiting hormone, is able to lower prolactin levels and restore gonadal function in more than 90% of patients with hyperprolactinemia who have not undergone a previous operation or irradiation. The effect of the therapy, however, persists only for the duration of treatment. This limitation is not itself a rationale for rejecting medical treatment, as it may be viewed as replacement therapy. By analogy we consider lifelong thyroxine therapy very satisfactory for treating hypothyroidism. Not only are prolactin levels lowered by bromocriptine but the vast majority of these tumors become smaller in days or weeks.[7,8] The effect again persists for only as long as therapy is continued, and the tumors usually increase in size when treatment is withdrawn.[9,10] The dilemma, therefore, has reversed itself. Originally it was argued that small tumors produced no compressive symptoms and, therefore, could be treated medically, while large tumors required surgical decompression even if they could not be cured. Now we realize that only the small tumors can be cured by surgical resection and medical and surgical results (from the major centers only) are comparable. The large tumors are often difficult to resect and postoperatively patients often suffer permanent pituitary deficiencies in addition to persistent hyperprolactinemia. Therefore, surgeons are now pretreating their patients with bromocriptine in the hope of shrinking the tumors to make them more surgically accessible. The hope is that this would improve the cure rate in the larger tumors. As yet no series of any size has been published to demonstrate whether or not this assumption is correct. I believe it is unlikely, since the large prolactinomas associated with the highest prolactin levels are usually invasive and shrinkage of the tumors may not allow any better clearance of cells that have invaded either the periosteum, dura or cavernous sinus. On the other hand, if the tumor is shrunken into the fossa, the tumor may be decompressed more easily; thus the morbidity of the operation and the incidence of hypopituitarism may be reduced.

The question "why operate?" has to be asked when a tumor is shrunken, compressive symptoms have resolved, prolactin levels lowered and gonadal function restored with bromocriptine. One answer would be that once treatment is stopped the condition will recur. In itself this is true but in my view is not justification for a surgical procedure. If a patient chooses not to take lifelong dopamine-agonist therapy, then surgical

treatment is clearly indicated. However, if a patient understands that she or he will need to undergo lifelong medical therapy, then in my view medical therapy alone is a reasonable approach. Others have suggested that these patients should undergo external pituitary irradiation after the tumor has been treated with medical therapy. In this way medical therapy may be stopped after several years and the condition may not recur. This is speculation, however, and has yet to be proved. Additionally, the risk of development of hypopituitarism must be considered.

What about asymptomatic patients who are amenorrheic and have mild hyperprolactinemia; should they be treated? Such patients should at least be offered a short (six months) course of medical therapy. When they are euprolactinemic they often recognize an increase in their general well-being and libido. It has also been suggested that these patients, left untreated, may suffer from the adverse effects of estrogen deficiency and therefore deserve to have their gonadal function restored to prevent development of premature osteoporosis. The data are suggestive but do not prove that these patients have an increased incidence of thinning of the bones.

The prolactinoma story is still evolving. Perhaps in another ten years we will have answers to the perplexing questions that give rise to the controversies of the management of this important condition.

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Surgical Treatment for Congenital Heart Disease—Is It Corrective?

IN THE FOUR DECADES since surgical repair of congenital heart disease became common practice, the ingenuity of cardiovascular surgeons and pediatric cardiologists has made most lesions amenable to some form of surgical procedure. It has been acknowledged that some of these procedures are palliative, but the term "corrective surgery" has been applied increasingly, with the implication that closure of a defect or relief of an obstruction will return a patient to normal function. Unquestionably, most patients show relief of symptoms and improvement of exercise tolerance after an operation, but what is their long-term outlook?

Dr Perloff and his colleagues address this question in this issue, using a common lesion, tetralogy of Fallot, as a basis for discussion of problems that may be encountered after surgical "correction" of congenital cardiac lesions. It is recognized that following a surgical procedure, there may be residual lesions that are not evident clinically—such as small defects due to incomplete closure, or minor to moderate degrees of obstruction—and that serious complications such as complete heart block may result. However, there is an increasing realization that more subtle changes, which may have existed before or may present following the surgical procedure, could seriously interfere with patients' well-being and influence life expectancy. Also, persons with certain conditions have a high incidence of associated lesions that may not be diagnosed by routine physical examination, but that require continuing surveillance. Thus it is well known that up to 85% of patients with aortic coarctation have a bicuspid aortic valve,[1] which makes them susceptible to infective endocarditis.

Cardiac arrhythmias are not infrequent after an intracardiac operation; ventricular conduction disturbances and ventricular arrhythmias are common after repair of ventricular septal defects, tetralogy of Fallot and more complicated intraventricular anomalies, whereas surgical repair for atrial septal defects or insertion of an atrial baffle for aortopulmonary transposition predisposes to supraventricular tachycardia or sinus node dysfunction. Sudden death, which may occur months or even years after a surgical procedure for tetralogy of Fallot, has been associated with persisting ventricular premature contractions postoperatively. Garson and co-workers have related this to incomplete relief of right ventricular outflow obstruction, with elevation of right ventricular pressure above 60 mm of mercury.[2] Certainly the frequency of postoperative atrial arrhythmias has varied greatly in different centers and surgical technique appears to play an important role in the incidence; increasing appreciation of cardiac electrophysiology with appropriate modifications of technique may greatly reduce the frequency of this sequela.

Ventricular function following repair of congenital heart lesions has become a subject of increasing interest and concern.[3] It is not too surprising that after an incision into the right ventricle to approach a ventricular septal defect or relieve infundibular stenosis in tetralogy of Fallot, some interference with right ventricular function may occur. However, right ventricular function has been reported to be impaired in some adults following closure of atrial septal defects.[4] The mechanisms respon-

sible for this disturbance in right ventricular performance have yet to be determined, but it is quite likely that prolonged volume overload may result in myocardial fibrosis. Myocardial fibrosis has been described in the right ventricle in patients who have had pulmonary stenosis and in the left ventricle of those with aortic stenosis.[5] The degree of fibrosis relates to the duration and severity of the obstruction and the magnitude of the ventricular pressure elevation. Although most persons who have had relief of these lesions do not manifest evidences of poor ventricular performance, it is not known what their long-term prognosis is. They may well be more susceptible to earlier influences of coronary arterial insufficiency and reduced life expectancy.

The concern that prolonged pressure or volume overload on a ventricle may lead to progressive and irreversible myocardial damage has led a number of pediatric cardiologists and cardiovascular surgeons to recommend an operation as early as possible. Their contention is that a possible small increased risk of operating on a young patient is outweighed by the potential benefit of avoiding progressive myocardial impairment. Furthermore, an increasing tendency has developed to operate on patients who have relatively mild lesions such as atrial septal defects with small left-to-right shunts or pulmonary stenosis with mild elevations of right ventricular pressure. It is unfortunate that little information is available regarding the rate of progression of myocardial injury in different lesions of variable severity. There is convincing evidence that late surgical relief of the left ventricular outflow obstruction associated with aortic coarctation may have an adverse effect on long-term outlook. Both Liberthson and associates[6] and Maron and co-workers[7] in analyzing large groups of patients documented a high incidence of residual arterial hypertension, as well as cardiovascular symptoms and signs, in those patients who had late surgical repair of the coarctation, as compared with those who were treated at 1 to 5 years of age. There was a high mortality at a young age in the group operated on late. Neither of these studies, however, adequately addresses the question of long-term outcome in relation to severity of the lesion. It is a disturbing thought that it is highly unlikely that the natural history of many congenital heart lesions, in relation to their severity, will ever be known as even patients with milder lesions are now being treated. We should appreciate that decisions regarding surgical intervention are often based on prejudices of individual physicians, rather than on reliable objective data on the long-term prognosis.

The concept that the earlier a surgical procedure is done, the better is the outlook for normal myocardial development, has stimulated performance of procedures during infancy. It has been suggested that in some lesions, such as pulmonary atresia with a poorly developed right ventricle, early surgical intervention in infancy to relieve the obstruction, thus permitting flow through the ventricle, may facilitate growth of the chamber. We should recognize that congenital cardiac lesions may have profound secondary effects on morphologic development of the circulation during fetal life. In a fetus, myocardial mass increases entirely as a result of increase in cell numbers, and even a stressed ventricle responds with hyperplasia rather than by the hypertrophy characteristic of a postnatal heart.[8] The postnatal behavior of a heart that has either increased muscle mass or decreased mass, with greater or lesser cell numbers, remains to be investigated. It is quite possible, however, that even if the basic anatomic congenital defect is corrected in the neonatal period, this may be too late to achieve normal myocardial development. Perhaps with the facility for diagnosing congenital heart lesions prenatally by echocardiography and the advances in intrauterine surgical techniques, we can anticipate correction of defects in utero.

Within the past decade, many complicated congenital cardiac lesions, which were amenable only to palliation, are now being corrected physiologically by the use of synthetic or biosynthetic materials. A valved conduit consisting of a synthetic flexible conduit into which is incorporated a porcine (Hancock) valve is used for truncus arteriosus or pulmonary atresia repair. These procedures have provided excellent short-term results, but when used in infants and children, the limitation of the size of prosthesis that can be inserted inevitably results in progressive obstruction. This is due not only to the relative narrowing associated with the increased cardiac output related to growth, but also results from intimal proliferation in the conduit and degenerative changes in the porcine valve. It is unfortunate that the smaller conduits used in infants are more prone to earlier obstruction, so that the mean age for development of stenosis serious enough to require an operation is about 3 years. In older children and adults, however, conduit replacement may not be required for eight to ten years and possibly longer.

In the past, few patients with complex lesions survived beyond infancy or early childhood, but the surgical innovations are permitting survival into adolescence and adulthood. An increasing number of these patients will require continuing surveillance. This raises a serious question regarding the provision of care. Few cardiologists who treat adults only have seen patients with these complex lesions and they have a limited understanding of the anatomic and physiologic abnormalities. Pediatric cardiologists will have to be prepared to continue to care for these persons as they grow older, or nonpediatric cardiologists will have to improve their knowledge about congenital heart disease.

Lest this discussion appear pessimistic, it should be pointed out that whereas formerly about 50% of patients with congenital heart lesions died before 15 years of age and many others were severely limited, surgical intervention has allowed most to live active lives and has greatly prolonged life. Their survival to adulthood has, however, introduced additional concerns about career opportunities, insurability, risks of pregnancy, incidence

of congenital heart disease in their offspring and necessity for continued medical surveillance. These issues have yet to be resolved.

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A Gateway to Biostatistics

ELSEWHERE IN THIS ISSUE appears the article "An Introduction to Biostatistics" by Sacks and Glantz. The authors present what is actually an annotated bibliography that gives an overview of the subject, with special emphasis on the interpretation of the results and conclusions of clinical studies as these are reported in the medical literature. Even a scanning of their commentaries brings home the fact that the conclusions reached in published papers too often are not supported by the given data when these are subjected to careful and critical statistical analysis. Some very reputable medical journals fall victim to such errors.

Perhaps it is time for researchers and clinicians alike to learn more about how to judge for themselves the accuracy of the conclusions reported in any given published paper. The paper by Sacks and Glantz may be viewed as a gateway to biostatistics for physicians who wish to learn more about how to evaluate what they read in the medical literature—even in this journal.

MSMW

Case Reports

Pemphigus Vulgaris and Plasma Exchange

Role of Intercellular Antibodies

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CLINICAL AND experimental evidence implicates intercellular IgG antibodies in the pathogenesis of pemphigus vulgaris.[1-3] Acantholysis in fresh skin explants has been produced experimentally by incubation of whole serum with the purified IgG fraction of serum from patients with pemphigus vulgaris.[4,5]

Clinical improvement has been reported to correlate with loss of acantholytic activity and decreased antiepithelial antibodies in pemphigus patients particularly when measured by direct immunofluorescence;[6] this has led to trials of treatment with plasma exchange.

A patient with active pemphigus vulgaris refractory to steroid therapy was treated by plasma exchange in an attempt to reduce pemphigus antibodies and bring about clinical remission. Plasmapheresis was effective in reducing antibody titers measured by both direct and indirect methods. This did not correlate with suppression of active disease.

Report of a Case

A 56-year-old Spanish-American woman presented with 30% of her body surface area covered with progressive bullae. These had been present for nine months and her scalp, face, trunk, extremities and oral and vaginal mucosa were involved. Her pemphigus vulgaris (shown by biopsy) started two years earlier and had been treated successfully with steroid injections and antibiotics at that time.

Initial histologic examination showed intraepidermal bullae with acantholysis of epidermal cells; direct immunofluorescence showed intercellular IgG deposits in the epidermis. Circulating epithelial antibody levels were 1:160 and 1:320 before the initiation of therapy. An antinuclear antibody test was negative.

Administration of 100 mg a day of prednisone was begun and increased to 120 mg after the first week, 200 mg after the second and 300 mg after the third without improvement. Plasma exchange (performed by B. Ferdinando, RN, D. Phillips, RN, and E. Wilson, RN, of United Blood Services, Albuquerque) was then started twice a week. Interruption of plasmapheresis and decrease of the prednisone dosage to 100 mg a day were required because of *Neisseria meningitidis* pneumonia. New bullae developed, but the pneumonia responded to treatment with aqueous penicillin G. Plasmapheresis and prednisone therapy were resumed, but new bullae continued to develop despite increases in prednisone dosage to 800 mg a day over a period of four weeks. Intramuscular aurothioglucose therapy of 50 mg a week, started at eight weeks, and cyclophosphamide at 50 mg per day, started after 12 weeks, did not prevent new bullae, and the patient died. Permismission for autopsy was denied. Death appeared to be related to both pneumonia associated with immunosuppression and active pemphigus.

Methods

Plasma exchange was accomplished using a continuous-flow process on the IBM 2997 cell separator. Two liters of plasma (approximately one plasma volume) were removed and replaced by 5% albumin, fresh-frozen single donor plasma and saline.

Before and after each plasma exchange, a serum specimen was assayed for intercellular antibodies by indirect immunofluorescence using a technique described by Beutner and co-workers.[7] Monkey esophagus was used as substrate. A positive control pemphigus serum as well as negative control serum were used to test the substrate. The serum was tested, beginning at 1:10 and 1:100 dilutions. Studies were carried out in the laboratory of K. S. K. Tung, MD (Albuquerque).

Tissue specimens for direct immunofluorescence were obtained from perilesional skin and processed by the technique of Beutner and associates.[7] Commercially available goat antihuman IgG, IgM, IgA and C3 and fibrinogen with a fluorescein-to-protein ratio of 3.0 ± 0.5 to 1 were used. Tissue specimens for direct immunofluorescence were taken of perilesional skin with a 4-mm punch biopsy and transported in a citrate buffer solution containing ammonium sulfate, *N*-ethyl maleimide and magnesium sulfate.[8] Direct immunofluorescence testing was always carried out within one week in the laboratories of K. S. K. Tung, MD, and D. L. Tuffanelli, MD (San Francisco).

Serum samples were sent to Dr John R. Schiltz, Case Western Reserve University, Cleveland. IgG was prepared from the pooled samples and tested for ability to cause acantholysis in cultured normal human skin.[4]

Results

The titers of circulating intercellular antibodies before and after the plasmapheresis are illustrated in

Refer to: Johnson DW, Simon TL, Chapman WG: Pemphigus vulgaris and plasma exchange—Role of intercellular antibodies. West J Med 1983 Nov; 139:708-710.

From the Division of Dermatology, Department of Medicine (Drs Johnson and Chapman), the Division of Hematology-Oncology, Department of Medicine, and the Department of Pathology (Dr Simon), University of New Mexico School of Medicine, and United Blood Services (Dr Simon), Albuquerque.

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Reprint requests to Toby L. Simon, MD, Dept of Pathology, University of New Mexico School of Medicine, Albuquerque, NM 87131.

Figure 1. The titer of intercellular antibodies, as high as 1:320, dropped by two dilutions, a reduction of approximately 50% in circulating levels of antibodies, with each treatment. A rebound was seen following the first two procedures but not thereafter. Following the seventh procedure, levels consistently remained negative.

Tissue initially showed direct immunofluorescence. Ten weeks later, when the patient had active pemphigus vulgaris but indirect immunofluorescence testing was negative, specimens were negative for direct immunofluorescence.

IgG prepared from the original pool caused suprabasilar acantholysis after 72 hours in culture.

Discussion

Exchange plasmapheresis has been used successfully in patients with pemphigus vulgaris.[9-13] Four of the five patients reported responded on various schedules of plasma exchanges with various accompanying immunosuppressive drugs. The one patient in whom the therapy failed had disappearance of antibodies, but treatment was terminated due to problems with vascular access.[13]

The role of the IgG antibody in the pathogenesis of pemphigus has been shown by its ability to produce histologic lesions in vitro,[5] cause loss of adhesion in cultured mouse epidermal cells,[14] detach mouse epidermal cells grown in serum[15] and induce disease in mice by passive transfer from patients.[3] Moreover, a proteolytic enzyme recovered from cultures with the antibody has been termed "pemphigus acantholysis factor."[16] The hydrolysis of the cell surface by pemphigus acantholysis factor may result in loss of adhesion and ultimate acantholysis. Naturally occurring inhibitors to this action have also been described.[15]

Our patient's failure to have reduction of disease activity with decrease in serum levels and disappearance of tissue levels of intercellular antibody suggests that removal of antibodies may not be adequate therapy. This report confirms a previous observation[6] that the circulating antibody level measured by indirect immunofluorescence as a marker of disease has limitations in the setting of plasma exchange. Unlike in other reports, the change from positive to negative in direct immunofluorescence of perilesional skin did not correlate with clinical success.

Moreover, plasma exchange therapy was not clinically successful. Possible explanations for our lack of success include the following: (1) Circulating plasma inhibitors may have been removed along with the antibody. (2) The antibody may be a marker of the disease rather than truly pathogenic. (3) The patient's disease, which was unresponsive to all therapy, may have been too advanced to draw a conclusion from this trial of plasma exchange.

The antibody was shown to be active in the tissue culture system; therefore, it is surprising that its disappearance was not associated with clinical improvement. High doses of prednisone (given after plasma exchange treatment to prevent removal) combined with plasma

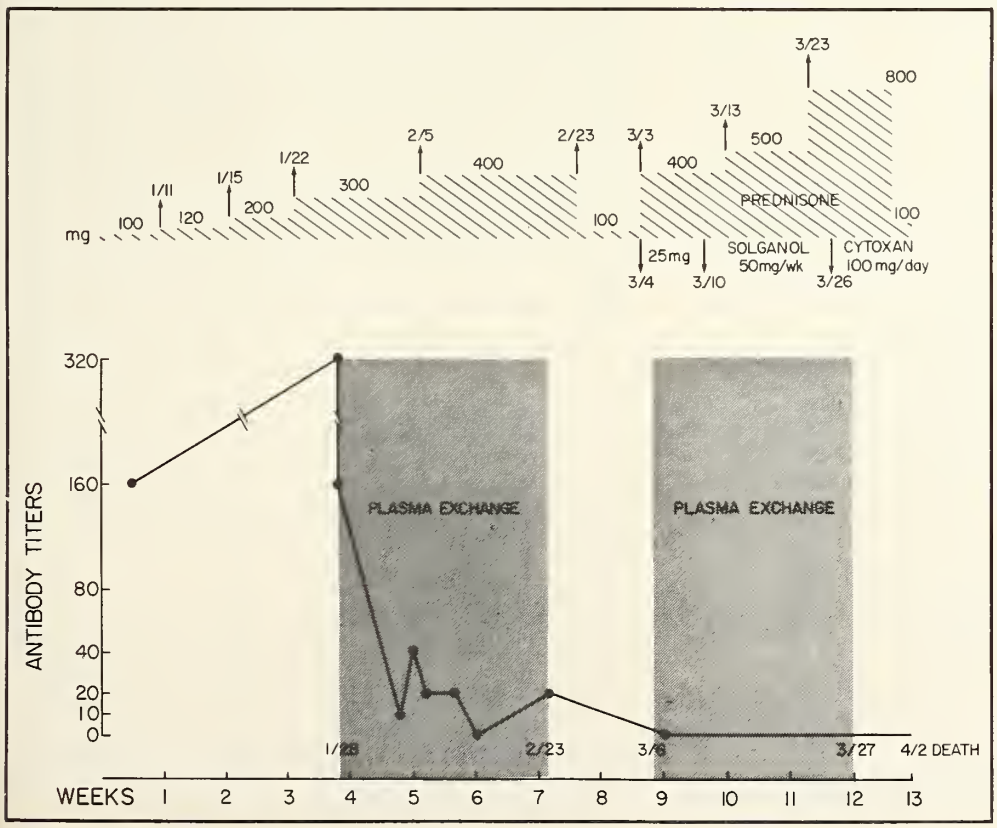

Figure 1.—The patient's clinical course, circulating antibody titers and treatment are shown.

exchange were not clinically effective; gold and cyclophosphamide added sequentially because of treatment failure were also ineffective. Ultimately the patient died with new bullae appearing in previously normal skin and previously healed areas along with crops of blisters. The role of the pemphigus antibody in vivo even when active in tissue cultures in vitro is therefore less certain than is implied in recent studies.[3] Factors other than the antibody, such as certain enzymes,[14] may be important in pathogenesis of this disease.

The role of plasma exchange, used in this case exhaustively over two months, is uncertain. Whereas it has been rapidly successful in other cases,[9-13] it did not prove of clinical benefit in this case. However, this patient failed to respond to any known treatment modality; thus, plasma exchange is not disproved as a possibly successful therapeutic maneuver. The combination of successful antibody removal with lack of clinical success suggests that the mechanism of any benefit found may be more complex than antibody removal. Indeed, the data in this case suggest that when plasma exchange therapy is used, certain markers of disease may lose their clinical value. The procedure can conceivably remove such markers without providing clinical benefit. Thus, clinical benefit that occurs after plasma exchange in many diseases should not be assumed to be due to removal of pathogenic substances.

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Toxic Shock Syndrome Due to Occult Postoperative Wound Infection

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DURING THE past several years, both the public and the medical community have come to know toxic shock syndrome as a potentially lethal symptom complex associated with tampon use in menstruating women. From the first report defining the syndrome,[1] the link with tampon use has been emphasized.[2-13]

There has been debate about whether toxic shock syndrome represents a new disease or merely a significant increase in a formerly unrecognized disease entity.[14] It does bear some similarity to staphylococcal scarlet fever in that both syndromes are associated with staphylococcal bacteria and skin rash formation.[14-20] However, staphylococcal scarlet fever does not cause the remainder of the clinical spectrum of toxic shock syndrome, and it does not show particular association with tampon usage. In fact staphylococcal scarlet fever has been reported in association with a wide range of staphylococcal infections, including empyema, fasciitis, subcutaneous abscess, peritonsillar abscess, mucus membrane colonization and septic abortion.[20]

While attention has been given primarily to tampon usage in association with toxic shock syndrome, recent reports have been published describing nonmenstrual causes.[20-32] Several cases have been associated with postoperative staphylococcal wound infections.[22,24-28]

A striking feature of the postoperative staphylococcal infections resulting in toxic shock syndrome, however, is that signs of local wound infection are rarely present.[8] These patients may present with generalized systemic symptoms, and the fact that a surgical wound infection might be the cause may easily be overlooked. It is therefore crucial that all physicians be aware of the possibility of occult localized infection in patients with symptoms of the syndrome, particularly those in whom a surgical procedure has been done recently. The case presented below illustrates the difficulty this may entail.

Report of a Case

A 35-year-old woman presented to the emergency department with complaint of nausea, vomiting, diarrhea and a rash. Approximately six months earlier she had undergone bilateral augmentation mammoplasty. Over the next few months she noted thinning of the skin over the right implant, which was considered possibly secondary to steroid in the outer lumen of the

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double-lumen prosthetic implant. One week before emergency admission, the right implant was removed and a new one inserted without steroid.

Four days following the revision procedure, the patient noted a sore throat, fever and mild swelling of her hands. The following day diarrhea and a rash developed. Her breasts were examined on the next day; no sign of wound infection was present, but she was started on a regimen of cephadroxil (Duricef). All symptoms continued, however, and a headache developed as well.

She came to the emergency department on the seventh postoperative day, three days after the onset of symptoms. Her menstrual period had begun that morning, and she had inserted a tampon.

On physical examination the patient was conscious but lethargic and there was pronounced tachypnea. Her temperature was 36.9°C (98.4°F) orally and 38.5°C (101.3°F) rectally. The rectal temperature rose to 38.9°C (102°F) several hours later. Pulse rate was 140, respirations 40 and systolic blood pressure 60 mm of mercury measured by Doppler device. A macular erythematous rash was present over the trunk, with vesicles and areas of superficial denudation over the extremities and buttocks. The skin was cool with a generally mottled appearance in addition to the distinct rash. Capillary filling was poor. The neck was supple, and no acute adenopathy was present in the cervical, axillary or inguinal regions. The oral mucosa was significantly dehydrated, but the posterior pharynx was not clearly seen due to an active gag reflex. Conjunctival injection and subconjunctival hemorrhage were present bilaterally. The recent surgical incision overlying the right breast implant was healing well with no sign of infection. Some rales were auscultated over the chest bilaterally, but cardiac examination showed no abnormalities. Bowel sounds were present and the abdomen was mildly tender throughout, but peritoneal signs were absent. On pelvic examination findings were within normal limits except for the presence of a tampon and a small amount of dark vaginal blood. Results of rectal examination were unremarkable; stool specimens were soft, gray and guaiac negative. Neurological findings were within normal limits except that the patient was quite lethargic.

An electrocardiogram showed sinus tachycardia at a rate of 140. On a chest radiograph mild bilateral basilar infiltrates were seen.

Laboratory data were as follows: blood gas findings with the patient breathing room air—pH 7.29, carbon dioxide pressure 19 mm of mercury, oxygen pressure 84 mm of mercury, bicarbonate 9 mEq per liter, carboxyhemoglobin 0.3%; electrolytes—sodium 135, potassium 5.3, bicarbonate 14 and chloride 94 mEq per liter; glucose 55 mg per dl; complete blood count—30,300 leukocytes per μl with 86% total neutrophils, including 54% nonsegmented neutrophils and 6% metamyelocytes, 6% eosinophils, 4% monocytes and 4% lymphocytes. Toxic granulation of the polymorphonuclear leukocytes was noted. Hemoglobin was 14.3 grams per dl and the hematocrit 41.1%. The platelet count was initially 121,000 per μl, but decreased to 14,000 per μl one day after admission. The amylase level was 378 IU per liter and creatinine 6.3 mg per dl. Analysis of urine showed a specific gravity of 1.027, pH 5, 2+ protein, six to nine leukocytes and seven to ten erythrocytes. Prothrombin time was 16.8 seconds with control of 10.5 seconds and activity of 25%.

The recent surgical incision over the right breast was surgically reopened and a small amount of clear serosanguinous material obtained. No organisms were found on Gram's stain, and the specimen was cultured for aerobic and anaerobic organisms.

Cultures were also obtained of specimens from the tampon, cervix, vagina, throat, stool, urine and blood. Catheters were inserted into the peripheral veins, right internal jugular vein and right femoral artery. A Foley urinary catheter was also placed.

Medications included dextrose (25 grams given intravenously), gentamicin (80 mg intramuscularly), methacillin (2 grams intravenously), high-dose steroid (dexamethamethasone, 96 mg intravenously) and an intravenous dopamine infusion in the α-adrenergic range at 15 μg per kg of body weight per minute. After 5 liters of crystalloid intravenous fluid, the central venous pressure was zero and arterial blood pressure by intraarterial monitoring device ranged from 60 to 80 systolic and 30 to 50 mm of mercury diastolic. A repeat chest radiograph showed increasing pulmonary edema, and repeat blood gas studies with 5 liters of inspired oxygen by nasal cannula showed pH 7.24, carbon dioxide pressure 27 mm of mercury, oxygen pressure 56 mm of mercury and bicarbonate 12 mEq per liter.

The patient was transferred from the community hospital emergency department to the intensive care unit of a nearby referral center. The diagnosis was severe infection complicated by shock and adult respiratory distress syndrome. The pattern was considered possibly compatible with toxic shock syndrome.

While there were no local signs of wound infection, and initial reopening of the surgical incision had showed no exudate, the right mammary implant was completely removed in an effort to find the source of infection. Underlying the implant was a collection of 15 to 20 ml of purulent material, which was cultured for aerobic and anaerobic organisms. The left mammary implant was removed as well, but no infection was found. Both wounds were irrigated, packed and allowed to heal by secondary intent.

Coagulase-positive *Staphylococcus aureus* was cultured from the exudate found below the right mammary implant; all other cultures revealed no growth. The patient had been treated empirically with intravenously given nafcillin, which was continued for a ten-day course.

Vascular collapse remained a problem for several days, requiring significant amounts of intravenous fluids as well as α-adrenergic pharmacological agents.

A total of 16 liters of crystalloid fluid was given during the first 36 hours. Support of blood pressure necessitated the simultaneous administration of norepinephrine, epinephrine, dopamine and neosynephrine during the first day, and the continuation of epinephrine and dopamine therapy for an additional two and three days respectively. Mean arterial pressure was initially 55 mm of mercury and stabilized in the 70 to 80 range by the fifth day. Central venous pressure was initially 5 cm of water and never exceeded normal limits.

Significant adult respiratory distress syndrome developed. The patient was intubated and placed on positive pressure ventilation. Positive end-expiratory pressure of 15 cm of water was required to maintain adequate oxygenation. Pulmonary capillary wedge pressure never exceeded 18 cm of water. Bilateral pleural effusions developed and were aspirated, showing sterile transudate. The patient's respiratory status slowly improved and she was extubated on the fifth hospital day.

Maximally abnormal laboratory values were as follows: complete blood count—45,200 leukocytes per μl; hemoglobin 10 grams per dl; 10,000 platelets per μl; fibrin split products between 80 and 160 μg per ml; prothrombin time 11.8 seconds with control of 17.4 seconds and activity of 23%; total bilirubin 8.2 mg per dl with direct bilirubin 5.7 mg per dl; highest unfractionated total bilirubin 9.3 mg per dl; serum aspartate aminotransferase 232 IU per liter; serum alanine aminotransferase 230 IU per liter.

The patient was discharged from hospital 17 days after admission, 20 days following the onset of symptoms and 24 days after the revision augmentation mammoplasty. The breast wounds were still open but granulating well. Several large areas of skin desquamation were present, particularly over the buttocks, but were healing without complication. Trace pitting edema was still detectable at the ankles. She has continued to do well since her hospital stay.

Discussion

The patient obviously had an overwhelming toxic illness accompanied by shock. The source of infection, however, was far from obvious. Symptoms and physical examination findings suggested a respiratory or gastrointestinal tract site. While her history of recent breast operations warranted exclusion of the mammary implant, there was strong evidence against the implant as a source of infection. There were no local signs such as erythema, warmth, tenderness, induration or fluctuance. Even the initial surgical reopening of the incision failed to reveal pus, and Gram's stain and culture of the clear serosanguinous material obtained found nothing remarkable. Only complete removal of the mammary implant revealed the site of infection.

The diagnosis of toxic shock syndrome might have suggested the tampon as an etiologic factor. However, symptoms began three days before the onset of menstruation, and the first tampon had been inserted only on the day of hospital admission.

TABLE 1.—*Definition of Toxic Shock Syndrome**

Fever—temperature $\geq$38.9°C (102°F)

Rash—diffuse macular erythroderma

Desquamation—one to two weeks after onset of illness, particularly of palms and soles

Hypotension—systolic blood pressure $\leq$90 mm Hg for adults or $<$5th percentile by age for children 16 years of age or younger, orthostatic fall in diastolic blood pressure $\geq$15 mm Hg from lying to sitting, orthostatic syncope or orthostatic dizziness

Involvement of at least three of the following organ systems:

- Gastrointestinal—vomiting or diarrhea at onset of illness
- Muscular—severe myalgia or creatinine phosphokinase level $\geq 2\times$ULN
- Mucous membranes—vaginal, oropharyngeal or conjunctival hyperemia
- Renal—blood urea nitrogen or creatinine levels $\geq 2\times$ULN, or $\geq$5 leukocytes per high-power field, in the absence of urinary tract infection
- Hepatic—total bilirubin, serum aspartate aminotransferase or serum alanine aminotransferase levels $>2\times$ULN
- Hematologic—platelets $\leq$100,000 per μl
- Central nervous system—disorientation or alteration in consciousness without focal neurological signs when fever and hypotension are absent

Negative results on the following tests if obtained:

- Blood, throat or cerebrospinal fluid cultures, although blood cultures positive for *Staphylococcus aureus* are accepted by some authors[32]
- Serological tests for Rocky Mountain spotted fever, leptospirosis or rubeola

ULN = upper limit of normal

*Adapted from Morbidity Mortality Weekly Rep.[4,19,32]

Treatment of menstrually related toxic shock syndrome consists of tampon removal and the use of a β-lactamase-resistant antibiotic.[7,33] The latter has been shown to reduce the rate of recurrence of menstrually related toxic shock syndrome.[7] While definitive data are unavailable, the use of a β-lactamase-resistant antibiotic would seem prudent for cases of postoperative toxic shock syndrome as well. The crucial treatment, however, is surgical drainage of the infected site as indicated. Had the source of infection not been identified, it might have seemed reasonable to treat our patient with antibiotics effective against enteric or respiratory tract organisms. However, failure to include a β-lactamase-resistant antibiotic—and failure to drain the infected site—might have been most unfortunate.

The case presented does conform with the criteria suggested by the Centers for Disease Control for toxic shock syndrome (see Table 1).[4,19,34] All four of the mandatory findings were present: fever, rash, desquamation and hypotension. Five of the secondary criteria were present as well: the disease involved the gastrointestinal tract, mucous membranes, kidneys, liver and platelets.

The patient's rash is of particular interest. While it does conform to the Centers for Disease Control criteria of diffuse macular erythroderma and desquamation, the vesicle formation and early denudation are not typical of toxic shock syndrome. They do occur, however, in the scalded skin syndrome, a disease which does not cause the full clinical spectrum found in both

toxic shock syndrome and the case presented. The rash in scalded skin syndrome is caused by the exfoliatin toxin produced by the particular staphylococcal phage type associated with the disease. The staphylococcal organism found in toxic shock syndrome is not known to produce this toxin.[11]

Only one other case of toxic shock syndrome following artificial implant has been reported,[29] and this case also involved a mammary implant. The patient died despite vigorous therapy with antibiotics, fluids and vasopressors and surgical removal of the infected implant.

Postoperative wound infection is a rare cause of toxic shock syndrome, accounting for fewer than 1% of all cases reported to the Centers for Disease Control between January 1, 1980, and July 31, 1981.[29] The truly dangerous aspect is that local wound infection is usually not obvious: signs of local infection were absent in 15 of 17 cases they reviewed.[20] The case reported here was particularly difficult to diagnose; even surgical reopening of the incision at first failed to reveal infection. Wound abscess was discovered only after the implant itself was removed. No physical signs or symptoms of wound infection were ever apparent until this final step was taken.

Conclusion

Local signs of wound infection are typically absent in postoperative toxic shock syndrome. The patient with apparent "flu-type" symptoms may thus present to a primary care or emergency physician rather than to the surgeon. It is crucial, therefore, for all physicians to maintain a high index of suspicion for wound infection in any postoperative patient with fever, rash, hypotension and other symptoms that might easily be dismissed as viral syndrome.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Sleep Apnea Studies

TO THE EDITOR: I am writing in regard to the article "Sleep Apnea: A Prospective Study," published in the August 1983 issue.[1] One of the conclusions of the article is that older patients may deserve routine assessment in screening for sleep apnea. In my opinion this falls into the category of treating a test rather than a patient. I believe that most sleep laboratories require (certainly ours does) oxygen desaturation as well as clinical symptoms to define a "syndrome of sleep apnea." In these days of efforts to try and control medical costs, routine screening of all types must be thought out very carefully and in particular a test that carries the kind of expense that routine apnea monitoring or screening would entail.

It is well recognized that both children and elderly patients have more sleep apnea. I think the data provided by monitoring a group of asymptomatic patients with sleep apnea in a research facility may be of value over the long term. This sort of data along with oxygen saturation monitoring associated with the prospective observation of these patients for the development of pathologic features such as sleep disturbance, sudden death, congestive failure or respiratory dysfunction will be of great help. I do think, however, that to make any recommendations for evaluation or therapy on the basis of this study would be a mistake.

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* * *

Drs Kreis, Kripke and Ancoli-Israel Respond

TO THE EDITOR: We certainly agree with Dr Overfield that physicians should treat the whole patient and not a single test. We also agree that portable screening recordings do not provide a complete apnea evaluation any more than a routine electrocardiogram provides a complete cardiac evaluation, and that one would not initiate a major treatment for sleep apnea such as long-term medication or head and neck surgical procedures without thorough clinical evaluation. If a clinical examination suggests that the patient may be suffering significant symptoms or significant cardiorespiratory impairment related to sleep apnea, then further testing such as all-night oximetry would be indicated.

Nevertheless, a portable screening recording would be sufficient by itself to provide clinical guidance in some areas. Hypnotic drugs and other sedatives should generally be withdrawn from patients shown to have several hundred episodes of apnea a night. In addition, such patients should be warned about the deleterious effects of drinking alcohol before sleep. Patients with obstructive apnea who are obese are likely to benefit from weight loss. If a patient with central apnea is receiving alkalinizing diuretics, addition or substitution of acetazolamide would be reasonable. Such simple and practical recommendations could be made on the basis of an inexpensive screening test.

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Chronic Arsenic Poisoning

TO THE EDITOR: The recent case report by Selzer and Ancel on chronic arsenic poisoning[1] underscores the importance of including toxicologic factors in our attempts at differential diagnosis. Unfortunately, valuable data were not included in the attempt to locate the source of the arsenic exposure in this case. The hair is particularly useful as a biopsy material in determining the time of exposure: each inch away from the root takes us back about two months in time so that sampling the hair over its entire length can yield time-related information.

I was surprised to find no follow-up testing to assure that toxic exposure had ceased. Finally, in view of the poor response to treatment, would it not be worthwhile to include testing of physiologic minerals (such as zinc, magnesium and manganese) with which heavy metals are known to interfere? Treating such mineral deficiencies can attenuate the toxic effects of heavy metals so our interest in them is quite practical from the clinical point of view.

RICHARD A. KUNIN, MD
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* * *

Dr Selzer Responds

To the Editor: I should like to make the following comments in response to Dr Kunin's letter to the editor.

A discussion detailing the search for a source of arsenic poisoning was intentionally excluded from our report in the interest of brevity and because we felt it to be tangential to the emphasis of the paper. The results of hair analysis, however, are indeed mentioned, and it was on this basis that we determined the subacute rather than chronic nature of the toxic exposure.

Law enforcement as well as occupational health and safety officials were notified and an examination of the home and work environment ensued. Family members also had their urine screened for heavy metals. While not involved in this undertaking, it was our understanding that a thorough investigation revealed no environmental toxic source.

We believed that the patient's response to chelation and his overall clinical course were typical of those described in the literature.[1] Given the results of the investigation, the patient's transfer to a nursing facility after hospital discharge and his continued gradual neurologic improvement, it was felt that the risk of reexposure was minimal. Hence, no follow-up toxicologic studies were performed. Adequate caloric and nutritional support was maintained during his recovery.

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Cellular Sodium Transport and Hypertension: A New Hypothesis

To the Editor: In Tuck's informative and interesting contribution "Sodium Transport in Hypertension" to the "Hypertension Symposium: Newer Topics on Normal and Abnormal Blood Pressure Regulatory Mechanisms"[1] the question is raised as to whether sodium transport abnormalities in erythrocytes "reflect the sodium and potassium ion transport capacity of more relevant target tissues such as vascular smooth muscle in essential hypertension." For obvious ethical reasons it is not feasible to study sodium transport in excised segments of human arterial wall. There are, however, several animal models where the hypothesis of abnormal sodium transport in vascular tissues has been tested.

In spontaneously hypertensive rats we found[2] an augmentation of the extracellular to intracellular Na^+ ratio in arterial wall attributable to a relative increment of extracellular Na^+. This change is consistent with a stimulation of the sodium-potassium pump; such an increase in pump activity in spontaneously hypertensive rats has been shown by Pamnani and co-workers.[3]

On the other hand, in arterial wall of rats with saline-induced hypertension we found[4] a diminution of extracellular to intracellular Na^+ ratio, thus suggesting an increment of Na^+ into cells. This would be consistent with decreased activity of the Na^+-K^+ pump; indeed such a decrease in pump activity for the saline model of hypertension has been shown by Pamnani and associates.[3] Once more, studies in animals help provide a sound physiopathological interpretation to clinical observations, which unavoidably have to be more limited in scope.

We earlier concluded[2,4] that hypertension may be related to changes in arterial wall smooth muscle electrolyte distribution and in a recent paper we presented

> the hypothesis, as provocative as it may appear, that the change from human essential hypertension to malignant hypertension may well be associated with a change in the vascular wall from increased extracellular Na^+ to augmented intracellular Na^+ caused by suppression of the Na^+-K^+ pump mediated by a superimposed agent, conceivably of the type of the demonstrated ouabainlike humoral factor.[5]

To close, there are three points I wish to emphasize: (1) As stated by Tuck in the symposium[1] it is now clear that hypertension cannot be regarded as a relatively uniform disease having one predominant cause. (2) I very much doubt that useful diagnoses or predictions in regard to hypertension may be obtained from studying sodium transport in nonsolid human tissues such as blood cells, particularly erythrocytes that, at least in humans, are incomplete and anucleated cells. Transport of Na^+, and other ions, must be studied in the arterial wall, which ultimately is the common pathway for the manifestation of hypertension. (3) That the principal ion transport aberration in essential hypertension may be an increase in *intra*cellular Na^+ appears too drastic a change; it can be surmised from cell physiology considerations that excessive intracellular Na^+ is far more harmful to cellular function than increased extracellular Na^+. Thus, our findings[2,4] combined with those of Pamnani and co-workers[3] on the Na^+-K^+ pump provide strong support for placing the increased Na^+, at least during the long, controllable phase of hypertension, in the extracellular space..

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Postoperative Complications

To the Editor: I was of course saddened to read in my local newspaper about the unfortunate death of a patient after having had a hemorrhoidectomy performed. It is also unfortunate to read in the newspaper that physicians are being quoted that patients "never" die from the operation or after a hemorrhoidectomy.

The unfortunate fact is that patients can die after any kind of operation; even the most minor surgical procedures do have some morbidity and mortality. I believe that physicians should be very careful with words such as "never" or "always."

The complication of infection, which the patient I have mentioned suffered, is not unknown after rubberband hemorrhoidectomy. As a matter of fact, this complication was discussed at a recent University of California postgraduate surgical program. One feels a great sympathy for the family and the patient and also for the attending physician. I write only to request that other physicians be very careful in the use of words such as "never" when they are questioned by the press about unfortunate surgical occurrences and postoperative complications. I have often thought that the loneliest man in the world is a surgeon whose patient has a postoperative complication.

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Some Less Obvious Causes of High Health Care Costs

To the Editor: There are several less obvious but nonetheless important causes of inflated health care costs that I, as the purchasing agent for my patients, should address and accept as my share of the responsibility for these costs. I will name three: respiratory therapy, coronary care units, intensive care units.

These ancillary hospital services are sometimes looked upon as fringe benefits of medical care, nice to have available, useful when needed and probably not too costly. Let us take a closer look.

Respiratory Therapy

In the mid-1960s there was an upsurge in respiratory therapy training programs. Before that time leg exercises, deep breathing, coughing and blow bottles had seemed to serve us well in preventing postoperative atelectasis and pulmonary emboli. But now, suddenly, I am remiss if I fail to order preoperative breathing exercises and the unit for the postoperative procedure given the title of "incentive spirometry."

All this has happened even though we have no documented evidence that such inhalation therapy is of any long-term benefit. In 1979 Dr John F. Murray editorialized as follows in the *New England Journal of Medicine:*

> No controlled studies have been performed to determine the prolonged influence of daily physiotherapy sessions of ventilation and gas exchange, the work of breathing and associated disability, and most importantly, the incidence of bronchopulmonary infections.

Looking at the bottom line, Blue Cross and Blue Shield are questioning whether the $4 billion paid out annually for respiratory therapy are dollars well spent. Should I, for my part, think twice before writing that "routine" order for inhalation therapy?

Coronary Care Units

Not too long ago coronary care units were found only in larger, metropolitan hospitals or teaching centers. Today every community hospital of even moderate size boasts of a CCU. These beautifully and expensively equipped units enclose the patient in a cocoon of electronic gadgetry, which beeps out the cardiac rhythms and disgorges endless strips of electrocardiographic tracings.

What a comfort to the patient to be constantly reminded that his most vital body functions are being closely monitored by this sophisticated machinery, and how reassuring for me to know that I am giving my patient the ultimate in medical care.

But is all this necessary? Just how much of this medical mothering is justifiable? One physician may insist upon 14 days in hospital for his coronary care patients, another follows a 10-day protocol, while still another is content with a 5-day stay. I am reminded of the Nottingham study in Great Britain reporting that relatively few patients with suspected myocardial infarcts are admitted to hospitals, yet their mortality statistics are comparable to ours. Who has the answer to this "big ticket" question?

Intensive Care Units

In the February 25, 1983, issue of *JAMA,* Hook and his associates reviewed the intensive care unit (ICU) statistics at Harborview Medical Center in Seattle.[1] They concluded that in pneumococcal bacteremia ICU support was of no benefit. They found, further, in reviewing earlier data, that the mortality and risk factors have not changed over the past two decades.

In the same issue of *JAMA,* Dr William Knaus editorialized, "To my knowledge, there is not a single scientific study claiming that, by itself, intensive care

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

unit (ICU) support cures any disease."[2] He agreed that ICU support can reduce the immediate risk of death in certain acute illnesses, and that it is valuable in burn cases. "But ICUs also make it possible to prolong the dying process. It is essential, therefore, to acknowledge an absolute limit to intensive care if we are to improve its use."

Who among us will have the courage to set down firm criteria for admission to an ICU?

This again brings us back to the issue of cost containment. Knowing that the use of respiratory therapy, CCUs and ICUs accounts for well over 1% of our gross national product, will I be able to curtail my appetite for these costly ancillary services or will I wait for Uncle Sam to put me on a diet? Will we physicians continue to make these decisions or will they be made for us by government appointed committees?

We are faced with this choice: Make a conscientious and consistent effort to use these costly services only when the absolute indication exists or be ready to have them limited for us. This can be our individual effort in our everyday practice. It will not be easy. We find it difficult to cut back on the full benefits of care our patients have learned to expect.

Even more difficult for us will it be to accept the fact that we need strong negotiators to represent us in Washington, DC. As physicians we have been reluctant to give up our individuality. Efforts to unionize us have failed. In spite of this, and not always with full support from physicians, the health care industry (as the practice of medicine is referred to in Congress) has had capable negotiators at work in the nation's capital. The vigorous efforts exerted by the American Medical Association in our behalf have not always been given the credit due them.

We in medical practice must realize that we are facing changing economic realities—it is no longer "business as usual." Our leaders who represent us at the bargaining table are aware of this. But they need negotiating tools. We can lend strength to these tools by asserting a readiness to trim some of the fat from our health care diet, while protecting a lean and healthy patient care program.

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Special Editor for Idaho

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Physicians and Boxing

To the Editor: The medical profession has been advocating the banning of boxing in the recent past because of some of the injuries incurred. Boxing will never be banned because if an attempt was made one could expect it to go underground.

Way back in the 1960s when I introduced the concept that a fighter could not be "saved by the bell" for obvious reasons, I also suggested that the medical profession become more involved in the sport to help it.

We can do a lot to minimize the injuries incurred in boxing if we can interest both neurologists and neurosurgeons in becoming seriously involved in the sport. We need more of those disciplines both as ring physicians and referees. If we could have these physicians acting as referees, we could add considerably to the sport's safety for they would recognize more problems than nonmedical referees. Let's put our mouths where our knowledge is.

One does not have to be a boxer to be a referee. The rudiments of the sport can be quickly learned from ring professionals and trainers, so this argument can be quickly forgotten. Remember, one of the finest football coaches and boxing coaches of all time was the eminent Dr John Bain Sutherland of the University of Pittsburgh. He neither played football nor boxed—and his accomplishments are legion.

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Topics in Primary Care Medicine

Clinical Aspects of Herpes Zoster

RICHARD B. GLASER, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Herpes zoster is a frequent, occasionally incapacitating and rarely fatal infection with *Herpesvirus varicellae* (varicella-zoster virus).

Zoster results from the reactivation of latent varicella-zoster virus in persons who at a younger age had suffered a primary varicella (chickenpox) infection. According to the widely accepted Hope-Simpson theory, based on epidemiologic and pathologic observations, the varicella-zoster virus enters cutaneous nerves during the primary varicella infection and migrates to the dorsal root or trigeminal ganglion where it remains dormant. If this homeostasis is somehow upset and the virus is able to replicate, herpes zoster develops. The efficacy of the host response then determines whether the infection remains localized to the dermatome innervated by the ganglion or becomes more widespread, involving other dermatomes, anterior horn cells or even viscera.

Predisposing Factors

Table 1 shows the factors predisposing to the development of herpes zoster. The most common factor predisposing for herpes zoster is age. The attack rate climbs with each passing decade and the infection is especially common after age 50. In 3,534 patients followed in England for 15 years, the overall incidence of zoster was 5.4%, rising to 16.2% for people in their ninth decade.

While it is true that certain neoplasms, especially lymphoproliferative disorders, do predispose to zoster, the converse is not true. People who have zoster are not significantly more likely to have a neoplasm than are age-matched controls. Hodgkin's disease is associated with an especially high incidence of herpes zoster, which has been reported to occur in 4.2% to 25% of patients with Hodgkin's. The higher incidence may reflect the effect of more aggressive therapy for this lymphoma in recent years. A strong association has been noted between therapeutic x-irradiation and zoster, and a recent study suggested that x-irradiation followed by chemotherapy posed the greatest risk to a patient with Hodgkin's disease. Other factors predisposing to zoster include local trauma, surgical procedures, spinal cord tumors and heavy metal poisoning. The findings of several studies indicate an increased incidence in patients treated with systemic corticosteroids or cytotoxic agents, but the magnitude of increased risk seems small in the absence of other risk factors such as irradiation or neoplasia.

Clinical Manifestations

The lesions of zoster begin as erythematous macules that usually evolve over 24 to 72 hours to form grouped vesicles. The rash usually begins posteriorly and moves anteriorly. New crops of lesions appear over one to four days and form crusts that last from two to four weeks. The severity of the eruption can vary from two to three vesicles to large confluent patches. Thoracic dermatomes are involved in about 50% of cases, the remainder being evenly divided between cervical, facial and lumbar dermatomes. About 20% of cases overlap adjacent dermatomes. In general, lesions do not cross the midline. While the major eruption is usually confined to one or two unilateral dermatomes, it is not uncommon to see as many as 10 to 20 vesicles in widespread, nonadjacent sites. This does not indicate dissemination. The rash is frequently preceded by a prodrome of four to five days' duration, characterized by neuralgia, pruritus and paresthesias. Pain in the absence of rash can be confused with myocardial

Refer to: Glaser RB: Clinical aspects of herpes zoster (Topics in Primary Care Medicine). West J Med 1983 Nov; 139:718-720.
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TABLE 1.—*Predisposing Factors for Herpes Zoster*

Increasing age
Local irradiation
Surgical procedure
Hematologic neoplasms and lymphomas
Rheumatologic disorders, such as systemic lupus erythematosus, rheumatoid arthritis
Cytotoxic chemotherapy

ischemia, peptic ulcer or biliary or renal disease. Rarely, the pain will not be followed by a rash *(zoster sine herpete)* As with varicella, the rash can cause significant scarring. Motor dysfunction caused by involvement of anterior horn cells occurs in about 1% of patients. The distribution of weakness almost always coincides with the involved sensory dermatome. Functional recovery occurs in 75% of affected persons. It is important to keep in mind the possibility of spinal tumors when motor paralysis complicates zoster, because tumors may be associated with both zoster and motor dysfunction.

Zoster involvement of the external auditory canal or tympanic membrane may be accompanied by homolateral facial paralysis (Ramsay-Hunt syndrome). This may be associated with loss of taste over the anterior two thirds of the tongue and disturbed lacrimation. Functional recovery is the rule, but occasionally neurologic regeneration is faulty, leading to profuse tearing during mastication (crocodile-tear syndrome).

Zoster involving the eye occurs in about a third of patients who have zoster of the ophthalmic division of the trigeminal nerve. There is close correlation between vesicles at the tip of the nose and eye lesions due to their common innervation by the nasociliary nerve. Anterior uveitis, secondary glaucoma, corneal scarring and postherpetic eye neuralgia may result from eye involvement. Ophthalmoplegia and ptosis may also occur and may precede the eruption.

Zoster encephalomyelitis is an uncommon manifestation of varicella-zoster infection, occurring from one week before to eight weeks after the cutaneous eruption. The onset is abrupt, with seizures, headache and a change in sensorium. Ataxia and cerebellar signs are frequent, and transverse myelitis may occur. A third of patients have a distinct syndrome of ophthalmic zoster and contralateral hemiplegia. Death is less common than with herpes simplex encephalitis, occurring about 25% of the time in untreated patients.

Zoster in an Immunocompromised Host

Patients who have disorders affecting humoral antibody responses, cell-based immunity or phagocytosis all seem to be at a greater risk for zoster developing. The disease is also more likely to take an aggressive form in such patients. In about 2% of otherwise healthy patients, and in up to 30% of immunocompromised hosts (almost invariably anergic), the disease disseminates widely. There may be involvement of the viscera as well as widespread cutaneous lesions. Symptomatic involvement of lungs, heart, central nervous system, gastrointestinal tract and serosa may occur. Such dissemination typically occurs from 4 to 11 days after the onset of localized lesions. Disseminated zoster in an immunocompromised host resembles varicella, with very low mortality. When there is serious underlying disease, mortality may reach 30% to 40%.

Children with no history of varicella, who are immunosuppressed or have widespread eczema, have fewer and less severe infections when treated prophylactically with zoster immune globulin after exposure. Interferon ameliorates the consequences of varicella-zoster infection in patients who have cancer. Whereas there seems to be considerable variability in *H varicellae* susceptibility to acyclovir, there are several anecdotal reports of its efficacy in disseminated zoster. There are as yet no controlled studies documenting the value of acyclovir in such situations.

Postherpetic Neuralgia

Postherpetic neuralgia is usually defined as pain lasting for two or more months after the resolution of cutaneous lesions. As many as 5% of patients with postherpetic neuralgia will have pain that persists indefinitely. Postherpetic neuralgia is unusual before age 40, but reaches an incidence of over 50% after age 60. Severe pain preceding or accompanying the eruption is associated with a greater likelihood of persistent pain following resolution of the rash.

In patients younger than 60 years, analgesics of sufficient strength should be used to make them comfortable. Patients older than 60 years should be considered for prophylaxis to prevent postherpetic neuralgia in addition to management of pain with analgesics. Corticosteroids, when administered soon after the onset of skin lesions, diminish the incidence of postherpetic neuralgia. In a controlled study, 73% of a control group and 30% of a corticosteroid-treated group had postherpetic neuralgia. The healing time of the skin was comparable in both groups, and there was no evidence of lesion dissemination in any of the steroid-treated patients. Prednisone is given in divided doses, 60 mg a day for one week, followed by 30 mg a day for one week and 15 mg a day for one week. Comparable corticosteroids may be used. Administration should be based on an analysis of the attendant risks as well as the benefits. For patients who have diabetes, hypertension, peptic ulcer disease, congestive heart failure or other infectious diseases, the relative risk may be too great to warrant using steroids.

For patients who have severe pain or a high risk of postherpetic neuralgia in whom corticosteroids are contraindicated, other less proved but potentially effective therapies are available (Table 2).

A 40% solution of idoxuridine in dimethylsulphoxide (DMSO)* applied continuously with a wet dressing to the affected dermatome for four days is used in Europe.

Levodopa, 100 mg given three times a day, in con-

*DMSO has not been approved by the Food and Drug Administration for this use in the United States.

TABLE 2.—*Treatment of Postherpetic Neuralgia*

Indications and Effect	*Drug*	*Treatment Schedule*
Prophylaxis		
Effective	Prednisone	60 mg a day for 1 week in divided doses 40 mg a day for 1 week in divided doses 20 mg a day for 1 week in divided doses
	Idoxuridine	40% in dimethylsulfoxide applied continuously to dermatome for 4 days
Possibly effective ...	Levodopa	100 mg, and benserazide, 25 mg 3 times a day, until pain subsides
	Dehydroemetine dihydrochloride	60 mg a day by injection until pain resolves (maximum 10 injections)
Treatment of Established Pain		
Possibly effective ...	Amitriptyline and substituted phenothiazine in therapeutic doses	
	Adrenocorticotropic hormone, 60 units given intramuscularly; repeat only if pain recurs after initial response	
	Chlorprothixene	50-100 mg given intramuscularly, then 50 mg by mouth every 6 hours for 7-10 days, or 50 mg by mouth every 6 hours for milder cases
	Transcutaneous nerve stimulation	

junction with benserazide, a peripheral decarboxylase inhibitor, 25 mg given three times a day, appears to abruptly alleviate symptoms and to possibly decrease the incidence of postherpetic neuralgia. In a group of 20 patients older than 60 years given dehydroemetine dihydrochloride, 60 mg daily intramuscularly, all had excellent relief of pain within nine days.

Established pain may be effectively treated using psychotropic drugs. Chlorprothixene (Taractan), 50 to 100 mg given intramuscularly in severe cases, followed by 50 mg by mouth every six hours for seven to ten days, was shown in one study to afford relief to 29 of 30 patients within 72 hours. Amitriptyline, 75 to 100 mg at bedtime, plus a substituted phenothiazine (such as perphenazine, 4 mg three times a day; thioridazine hydrochloride, 25 mg four times a day) is also effective. Transcutaneous electric nerve stimulators have worked in patients who have been refractory to other therapies.

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A Positive Approach to Smoking Prevention and Cessation

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One of a series of articles from western state public health departments

Smoking has been clearly identified as a causal or contributing factor in a number of chronic diseases. A recent Surgeon General's report stated that smoking is the single most avoidable cause of death in our society.[1] Any agent that plays such a prominent role in the pathogenesis of chronic diseases deserves close attention from public health officials and physicians. From 1965 to 1982 the percentage of adult Americans who smoke dropped from 42% to 33%. Continued success in smoking reduction will be the result of a team effort between physicians and health educators.

Role of Physicians

Current research in the United Kingdom suggests that physicians can significantly influence patients to stop smoking.[2] Russell and co-workers showed that physicians who took two minutes to firmly explain the risks of smoking, gave their patients a pamphlet on how to quit and warned of a follow-up on the patients' progress had 17 times as many patients quit smoking for an entire year as did the control group physicians.[3] Russell and colleagues calculate that each general practitioner could realistically induce 25 smokers in one year to quit.

Similarly, at a three-month follow-up, Raw reported a greater reduction in smoking among chest clinic patients who had been advised by their physicians to quit (39%), compared with nonintervention controls (17%).[4] Rose and Hamilton found a three-year 35.5% abstinence rate among high risk cardiovascular smokers who attended three 15-minute smoking education and counseling sessions with their physicians on how and why to quit.[5] This compares with a three-year 14.5% cessation rate among nonintervention controls.

Some physicians may be reluctant to discuss a behavior they perceive everyone understands and has freely chosen. Physicians should not overestimate a patient's understanding of the health risks of smoking. Many smokers have a vague belief that smoking can be harmful but their understanding is not specific. Rather than telling a patient smoking can cause cancer or cardiovascular disease, a brief explanation of *how* it causes these diseases can be more effective. Rather than discussing how cigarettes harm a human body, discuss how they harm the *patient's* body. Kuebler advocates having patients explain what they already know about the effects of smoking. The physician then corrects myths and fills in any gaps.[6]

Neither should physicians underestimate a patient's desire or ability to stop smoking. The Utah Statewide Risk Prevalence Study found that more than 80% of current smokers had tried to quit (Utah Department of Health, unpublished report). The survey also indicated that in Utah the number of ex-smokers exceeds the number of current smokers. Survey research by Schachter indicates we have greatly underestimated successful cessation rates.[7] Traditionally, cessation rates have been kept only on persons in a formal program. Schachter observed that participants in smoking-cessation programs are usually hard-core smokers who tried unsuccessfully to quit on their own. They are not representative of most smokers. Smoking-cessation rates appear to be much higher in the general public.

A Health Education Approach

A main thrust in health education is to prevent, or at least delay, the onset of smoking. In this field the Utah Department of Health has developed a program to identify and affect often-neglected variables that in-

Refer to: Mason JO, Lindsay GB: A positive approach to smoking prevention and cessation (Public Health and Preventive Medicine). West J Med 1983 Nov; 139:721-722

Dr Mason has been until recently the Executive Director and Mr Lindsay is the Risk Reduction Coordinator, Utah Department of Health, Salt Lake City. Dr Mason is now Director-Designate, National Centers for Disease Control, Atlanta.

Reprint requests to Mr Lee Shaw, Director's Office, Utah Department of Health, PO Box 2500, Salt Lake City, UT 84110-2500.

fluence youthful smoking behavior. About 230 Utah teachers in 13 school districts have attended an eight-hour smoking-cessation workshop conducted by the Utah Department of Health, Bureau of Health Promotion/Risk Reduction. The target population consists of fifth and sixth grade students, more than 15,000 of whom have been involved in the project.

The first component of the curriculum is health information. Students learn about the cigarette's role in the later development of cancer, emphysema and heart disease. A much greater emphasis, however, is placed on the immediate health, economic, aesthetic and social effects of inhaling a single cigarette.

The second component of the smoking curriculum is resistance to persuasion. Students are taught how to most effectively reduce or counter peer pressure to smoke. They learn a variety of appropriate responses and then practice resisting peer pressure in classroom role-playing situations. Research indicates that students exposed to this type of structured peer pressure are more resistant to real pressure in the outside world.[8]

The final component of the smoking curriculum is decision-making skills. Students are taught generic decision-making skills they can use in making non-smoking-related decisions. After they have learned this process they apply their knowledge to the personal issue of smoking. Students trained in these skills typically identify more social, economic, aesthetic as well as health reasons for not smoking than do students who receive traditional curricula.[9]

Other measurable outcomes of the program include increased knowledge about the immediate health consequences of smoking and an increased ability to recall, identify and use skills to resist peer pressure to smoke.[2,8] In states with a higher smoking prevalence among youths, similar programs have been able to prevent or delay smoking.[10]

Conclusion

The drop in the percentage of adult Americans who smoke represents a major achievement for physicians and public health educators. The example of physicians and their advice to patients have already helped approximately 33 million smokers kick the habit. As physicians continue to support effective health education programs and counsel with individual patients, there should be an even greater reduction in the nation's number one preventable cause of death.

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Special Article

Introduction to Biostatistics

An Annotated Bibliography for Medical Researchers

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Biostatistical methods have become thoroughly integrated into modern biomedical and clinical research. Nevertheless, every observer who has evaluated articles in medical journals has noted that as many as half the reported results were based on questionable statistical analysis. This situation, combined with the fact that most errors involve relatively simple statistical procedures, points to the need for researchers and practitioners to be able to personally judge the quality of the statistical analyses in what they read. Fortunately, there are several excellent papers and texts available for those interested.

Biostatistical concepts and techniques play a central role in the development and evaluation of medical knowledge. Results of clinical trials are summarized in statistical terms and many people believe treatments must produce changes with "$P<.05$" to be effective. Given this central role, one would expect that anyone who reads, writes or edits medical articles and books today would have a working knowledge of basic biostatistics. But that is not the case. Most practicing physicians have had little or no exposure to biostatistical concepts during their formal training and rarely are continuing education courses on the topic of introductory biostatistics available. In addition, most medical students receive only limited coursework in biostatistics. This situation is reflected in the results of tests given recently to medical and pediatric residents in which fewer than half understood such basic statistical concepts as P (probability) value or correlation coefficient.[1] Medical researchers do little better; articles have appeared over the years reviewing the quality of statistics in medical literature[2-5] that consistently show that almost half the papers in good journals misuse statistical methods and consequently report confusing or incorrect results. We will summarize and review the best of many excellent articles and books that discuss problems with and the proper use of biostatistics in medical practice.

Statistical procedures known as *tests of hypotheses* allow estimations of the likelihood of concluding by chance that two things are related when they really are not. Unless a test merely confirms an obvious effect or an investigator includes raw data, a reader cannot tell whether or not the findings support the author's conclusions. Ironically the errors are usually relatively easy to detect, such as not using a control group, not randomizing or misusing elementary tests such as the t (distribution) test. These errors in experimental design and misuse of simple statistical tests are especially important in clinical studies. Physicians may believe a new treatment has been proved effective when it has not. On the one hand, patients treated as a result of this error may gain no benefit. On the other hand, concluding that a new treatment does not work when it does could produce unnecessary delay in applying helpful therapy. It is important to remember, though, that there can be differences of opinion as to the best way to analyze some data. These differences arise because most statistical methods are based on relatively simple models of reality, so the results of statistical tests are only accurate to the extent that reality and the mathematical model underlying the test are in agreement.

The ability to judge the strength of arguments on behalf of or against a new diagnostic test or therapy will become more important as financial constraints on medical practice grow. Even for effective therapies, there has been relatively little systematic evaluation of precisely which patients they help. Thus, as resources available for medical care grow more slowly, health professionals will have to better identify which tests, procedures and therapies are of proved value. In addition to knowing whether two therapies are different, it

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will be important to know how large the difference is. Many of these issues are statistical as well as clinical. Biostatistics can provide the tools for turning clinical and laboratory experience into quantitative statements about whether, and by how much, a treatment affected a group of patients. The articles we review here point out the most common errors made in the design, conduct and analysis of studies; familiarity with any one of the books will increase one's understanding of the statistical language that has come to permeate the modern biomedical literature.

Journal Articles

1. *Schor S, Karten I: Statistical evaluation of medical journal manuscripts. JAMA 1966 Mar 28; 195:1123-1128*

For this classic paper, the authors critically evaluated ten of the most frequently read medical journals including *Annals of Internal Medicine, New England Journal of Medicine, Archives of Surgery, Journal of Clinical Investigation* and *Gynecology and Obstetrics.* They determined whether conclusions drawn were valid in terms of the design of the experiment, type of analysis done and applicability of the statistical tests that were or were not used. In all, 28% of the articles were acceptable, 5% should have been rejected and 68% of the papers should have been revised to correct errors before publication. Schor and Karten describe the 12 types of errors they found, together with informative examples and their practical importance. The errors were of the following types:

- No control group was used when a control group was necessary to draw valid conclusions.
- Sensitivity was measured but not specificity in evaluating a drug, treatment or diagnostic procedure.
- Statistical tests were improperly used.
- Improper conclusions were drawn though the proper test was used.
- Design of study was not appropriate for answering question.
- Statistical tests were not used when needed and appropriate because of study design.
- Many statistical tests were applied to the same data but probability values were not adjusted for this.
- Too much confidence was placed on negative results in studies in which sample sizes were small.
- A statement of significant differences was made without a description of the type of test applied or level of significance used.
- Conclusions were drawn but no statistical tests were done to justify conclusions.
- Tables and charts used were misleading.
- The data were improperly manipulated.

Even though this paper is nearly 20 years old, its message is still clear and cogent. The difficulties Schor and Karten describe can be found in any current journal.

2. *Glantz SA: Biostatistics: How to detect, correct and prevent errors in the medical literature. Circulation 1980 Jan; 61:1-7*

The two most common statistical errors in the medical literature are the misuse of the standard error of the mean and misuse of the t (distribution) test. The t test is the most commonly used statistical test of hypothesis and is appropriate for comparing two groups or a single group before and after treatment. The author explains how misapplication of the t test to compare more than two groups leads to significance levels (P values) that are misleadingly small. The practical consequence of this error is that researchers are likely to assert that the treatment they are studying produced more of an effect than the data justify. The difference between the standard deviation and the standard error of the mean is explained, as well as the meaning of the P value and how to identify common errors in the use of the t test. Also described are how to avoid errors in the use of the t test and the steps a reader can take to correct for such errors when interpreting results in published papers. This article has been very popular among cardiologists and cardiac surgeons.

3. *Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in Circulation Research. Circ Res 1980 Jul; 47:1-9*

In this article, which can be thought of as a companion to Glantz's article, Wallenstein and colleagues describe the statistical techniques that should be used instead of the t test for analyzing data from several common types of biomedical research studies. They discuss several methods for comparing multiple treatments (on both the same and different experimental subjects) and experiments in which several different factors are studied at once. When several groups are being compared simultaneously, it is appropriate to first test for overall differences using a technique known as analysis of variance. If this test shows a significant difference among the groups, one then does a multiple-comparison procedure—essentially a modified t test—to identify which groups differ from the others. Several simultaneous multiple-comparison procedures are discussed, including the Bonferroni, Tukey, Dunnett and Scheffé methods. Also explained are analysis of variance techniques for studies in which one examines the joint effect on the outcome of two (or more) experimentally controlled variables, known as the factorial design. Finally, the authors discuss repeated measurement, in which the effect of treatments over time are studied. Each of these designs and techniques is illustrated with examples taken from papers published in recent issues of *Circulation Research.* When several methods are available to analyze results, the authors present them all and compare the results, together with the methods used in the original paper.

4. *Freiman JA, Chalmers TC, Smith H Jr, et al: The importance of β, the type II error and sample size in the design and interpretation of the randomized control trial. N Engl J Med 1978 Sep 28; 299:690-694*

In this article 71 "negative" clinical trials are examined that were published between 1960 and 1977

in journals such as the *New England Journal of Medicine, Journal of the American Medical Association* and *Lancet* to determine whether or not the investigators had studied samples large enough to have a reasonable chance of detecting a treatment effect if there was one. The authors present an excellent discussion of the statistical aspects of choosing a sample size for randomized controlled clinical trials. The choice of sample size involves controlling the risk of reporting a treatment effect when the treatment really has no effect (type I or α error) and the risk of missing a clinically significant effect (type II or β error). The power of a statistical test (power $= 1 - \beta$) is the probability of correctly recognizing true differences. A test's power depends on the size of the therapeutic effect the investigator would like to detect, the risk of erroneously asserting a difference (type I error) and the sample size.

The 71 trials were reexamined to determine whether the studies had a high probability (or power greater than 90%) of detecting both a 25% therapeutic improvement and a 50% therapeutic improvement. The authors found that 67 of the 71 trials had more than a 10% chance of missing a 25% response to treatment and 50 of the 71 had more than a 10% chance of missing a 50% improvement. They conclude that investigators often work with sample sizes that are too small to offer a reasonable chance of correctly rejecting the null hypothesis in favor of the treatment. The confidence interval for the size of a treatment should be considered, rather than simply focusing on the yes-no approach to hypothesis testing. Freiman and co-workers give an extremely clear presentation of this important issue.

5. *Reed JF III, Slaichert W: Statistical proof in inconclusive 'negative' trials. Arch Intern Med 1981 Sep; 141:1307-1310*

Like Freiman and associates, the authors reviewed several major medical journals *(American Journal of Surgery, American Journal of Medicine, New England Journal of Medicine, American Journal of Cardiology, Journal of Pediatrics* and *American Review of Respiratory Disease)* to determine whether or not investigators had studied samples large enough to detect clinically significant treatment effects.

After examining 335 articles from the six journals, Reed and Slaichert found that there was a 14% chance of detecting a "small" effect, a 39% chance of detecting a "medium"-size effect and a 61% chance of detecting a "large" effect. They conclude that research studies in medicine often involve such small samples that they lack adequate power to detect clinically significant treatment effects.

In planning an experiment researchers should specify the size difference they consider clinically important, how certain they wish to be when concluding that the treatment had an effect (type I error) and the test's power—that is, its probability of being able to detect this difference. If they find no statistically significant differences between groups using these criteria, then they can comfortably conclude that there are no clinically significant differences between the groups.

6. *Rothman KJ: A show of confidence. N Engl J Med 1978 Dec 14; 299:1362-1363*

In this short but important editorial Rothman argues for the use of the confidence interval in the presentation and interpretation of research results. Researchers should choose a measure (such as the odds ratio) that quantifies the degree of association or size of experimental effect in their data and then calculate a confidence interval around that measure. They will then have summarized the strength of association in their data and allowed for random variation in a simple and unambiguous way while reducing the problem of accept-reject logic implicit in statistical hypothesis testing. Whereas hypothesis tests force investigators to decide whether or not they found a "statistically significant" effect regardless of clinical significance, giving a confidence interval permits one to describe the degree of treatment effect as well as to quantitatively suggest clinical differences, even though the sample size may have been too small to provide enough power to conclude that the differences seen were "statistically significant."

7. *Mainland D: Medical statistics—Thinking vs arithmetic. J Chronic Dis 1982; 35:413-417*

Mainland discusses the problems associated with the ready acceptance and use by medical investigators of statistical "cookbook recipes" without understanding the concepts underlying these techniques. He raises two key questions: First, if medical researchers do not know the meaning of the analysis of their data, how do they know they have collected data in such a way that the analysis is valid? Second, how do they know that the analysis answers the questions that the research proposes to answer? In discussing these two questions, Mainland contrasts statistical thinking (concern with variability and the risks of bias) with statistical arithmetic (manipulation and testing of figures). He also reviews the concept of the P value and tests of significance. The initial use of "$P<.05$" to draw the conclusion that a treatment had an effect is presented using some of R. A. Fisher's original quotations. Investigators and readers who have come to view $P<.05$ as a sharp division between demonstrating and failing to demonstrate an effect will find Fisher's reasons for selecting this cutoff unsettling.

8. *Sackett DL: Bias in analytic research. J Chronic Dis 1979; 32:51-63*

In this article Sackett discusses the kinds of biases that arise in analytic studies, especially case-control studies. The focus is on biases that affect the specification and selection of a study sample and the measurement of exposures and outcomes, together with specific examples of each type of bias and how it can affect research results.

- Prevalence-incidence (Nyman) bias: If there is a time lag between exposure and the selection of study

subjects, then a delayed look at those who were exposed early will miss fatal and other short episodes and cases in which evidence of exposure disappears soon after onset of disease.

- Admission rate (Berkson) bias: When the admission rates to hospital of exposed and nonexposed patients and controls differ, the relative odds of exposure to the proposed cause will be distorted.
- Detection signal bias: An "innocent" exposure may become questionable if, rather than causing the disease under study, it causes a symptom that results in a vigorous search for the disease.
- Nonrespondent bias: Nonrespondents in a sample may have different exposure histories than the respondents.
- Membership bias: Membership in a specific group (for example, runners) may imply a level of health that is different from that of the general population.
- Diagnostic suspicion bias: Knowledge of a subject's prior exposure to a hypothesized cause can influence the diagnostic process.
- Exposure suspicion bias: Knowledge of a patient's disease state can influence the examination into possible exposure to the hypothesized cause.
- Recall bias: The recall memory of patients and controls may be different in both accuracy and amount of information.
- Family information bias: A new case of disease in a family stimulates information from other family members about exposure and disease.

Sackett suggests that one can prevent measurement biases by using interviewers who are ignorant of a subject's diagnosis, establishing objective criteria for exposure and outcome and obtaining information about exposure from independent sources. Methods for preventing sampling biases are more difficult and other than achieving high response rates, overcoming the other biases often means switching from case-control to cohort studies—which themselves have cost and time disadvantages.

9. *DerSimonian R, Charette LJ, McPeek B, et al: Reporting on methods in clinical trials. N Engl J Med 1982 Jun 3; 306:1332-1337*

The authors studied the reporting of important methodologic aspects in the design and analysis of clinical trials published in four general medical journals *(New England Journal of Medicine, Lancet, Journal of the American Medical Association* and *British Medical Journal).* They determined the frequency with which 11 methodologic items were reported in 67 clinical trials: the criteria for admission to the trial (37%), whether eligibility criteria were applied before assignment to treatment (57%), information about random allocation (84%), mechanism used to randomly assign (19%), patients' "blindness" to treatment (55%), "blind" assessment of outcome (30%), treatment complications (64%), numbers and reasons for follow-up (79%), statistical analysis beyond descriptive statistics (93%), descriptions of statistical methods used in data analyses (85%) and power of the studies (12%). The authors extensively discuss the importance of each item and why the nonreporting of an item may pose problems for a reader who is attempting to critically evaluate a clinical trial.

10. *Altman DG: Statistics and ethics in medical research. Br Med J 1980; 281:1182-1184; 281:1267-1269; 281:1336-1338; 281:1399-1401; 281:1473-1475; 281:1542-1544; 281:1612-1614; 1981; 282: 44-47*

This excellent series of eight short articles focuses on practical questions surrounding the use of biostatistical methods in medical research, especially clinical trials. The organizing theme of these papers is that poor design and erroneous analysis in research is unethical because such errors needlessly put human subjects at risk in invalid studies and mislead other investigators and practitioners by publishing incorrect results. The articles include examples from medical journals to illustrate the technical points and they are filled with good practical advice. The individual articles are "Misuse of statistics is unethical," "Study design," "How large a sample?" "Collecting and screening data," "Analysing data," "Presentation of results," "Interpreting results" and "Improving the quality of statistics in medical journals."

11. *Gore SM: Statistics in question: Assessing clinical trials. Br Med J 1981; 282:1605-1607; 282:1687-1689; 282:1780-1781; 282:1861-1863; 282:1958-1960; 282:2036-2039; 282:2114-2117; 283:40-43; 283:122-124; 283:211-213; 283:296-298; 282:369-371; 283:426-428*

Gore SM: Statistics in question: Assessing methods. Br Med J 1981; 283:486-488; 283:548-550; 283: 600-602; 283:711-713; 283:775-777; 283:840-843; 283:901-905; 283:966-969

This series of articles discusses practical and theoretic issues in the design, execution and interpretation of clinical trials and related statistical methods. The author uses a question and answer format and makes extensive use of graphics to clearly illustrate her points. Topics covered on clinical trials include trial design, randomization, double-blind trials, protocol monitoring and things that can go wrong in a clinical trial. Topics covered on statistical methods include descriptive statistics, transforming data, significance testing, confidence intervals, survival analysis and analysis of many variables. This series is an excellent starting point for anyone embarking on a research study involving data analysis and will also help clinicians understand basic statistical principles as well as issues in clinical trials.

12. *O'Brien PC, Shampo MA: Statistics for clinicians. Mayo Clin Proc 1981; 56:47-49; 56:126-128; 56: 196-197; 56:274-276; 56:324-326; 56:393-394; 56: 452-454; 56:513-515; 56:573-575; 56:639-640; 56: 709-711; 56:753-754*

This series of 12 short articles is designed to ac-

quaint physicians with the language of statisticians and to enable them to communicate more effectively with statisticians. Both descriptive and inferential statistics are discussed as well as issues relevant to medical research. This series is a clear introduction to many of the basics of statistics and several of its limitations. It also covers scattered diagrams, estimation from samples, paired t test, two-sample t test, regression, comparing two proportions, evaluating a new diagnostic procedure, normal values, survivorship studies and sequential methods. These articles focus on statistical computations rather than the broader issues discussed in the series by Altman and Gore.

13. *Altman DG: Statistics in medical journals. Stat Med 1982; 1:59-71*

In this comprehensive paper, the author takes the stance that the general standard of statistics in biomedical journals is poor and he considers four questions related to this premise.

- *What types of errors are made?* A brief list of errors commonly made in all areas of a research paper is given—design, analysis, interpretation and analysis of results—and one or two specific examples from published papers are provided. Errors in the design section include the use of too small a sample to get reliable results and the use of an inappropriate control group. Errors in analysis include the misuse of the t and x^2 tests, exclusion of subjects from analysis on the basis of the study's results and misuse of correlation analysis. Errors in interpretation include overconfidence in negative results and mistaking statistical significance for clinical significance. Problems with presentation of results include "spurious precision" and ambiguity, such as not stating whether a table contains the standard error or the standard deviation.
- *Why are standards so low?* There are several reasons why standards are low: Often no one knowledgeable about statistics has been involved in a research study. Also, the training many statisticians receive is not practical enough and often fails to include the methods relevant to biomedical data. Investigators have developed a preference for tests of significance and such tests tend to be given undue importance. Human experimentation committees approve poorly designed research and there is not enough statistical refereeing in the medical journals.
- *What are the consequences of the misuse of statistics?* Misusing statistics leads to inconveniencing or putting subjects unnecessarily at risk, diverting important resources from well-designed research and misleading other scientists.
- *What can be done to raise standards?* In the short term, the author proposes that journals institute the statistical refereeing of papers and develop comprehensive statistical guidelines for prospective contributors. In the long term, he proposes changes in statistical education to emphasize problem-solving rather than cookbook methods. He also suggests improving the composition of human subject committees so that inferior studies are not approved.

14. *Feinstein AR: Clinical biostatistics. Clinical Pharmacology and Experimental Therapeutics (ongoing series)*

This ongoing series of essays probes a wide variety of practical and philosophical issues surrounding the use of statistical techniques in biomedical research. The series is not especially good for learning basic statistical techniques, but consistently highlights important distinctions between statistical and clinical judgment and helps build bridges between the two. The series provides stimulating reading for those who already have some knowledge of basic statistics and would like to learn about issues that go beyond the details of statistical arithmetic.

Books

These books are listed in approximately increasing order of technical difficulty and use of mathematics, though all can be considered introductory in that they can be used in a first course in biostatistics.

1. *Glantz SA: Primer of Biostatistics. New York, McGraw-Hill, 1981* (reviewed by S.T.S.)

This very readable book contains fewer mathematical equations, formulas and tables than most statistics texts. It differs from other introductory books on biostatistics in three ways: It is based on the premise that much of what is published in the biomedical literature uses dubious statistical practices and the author attempts to alert readers to common errors in the literature; it contains an introductory section on multiple-comparison testing, and it is organized around hypothesis testing and estimation of the size of treatment effects, as opposed to the more traditional organization based on the development of statistical theory. The book also has a very effective chapter entitled "What does 'not significant' really mean?" which contains a practical discussion of statistical errors (types I and II) and the concept of the power of a statistical test. Most of the examples throughout the book are taken from interesting studies and problems (also based on examples from the literature) are included at the end of each chapter.

2. *Colton T: Statistics in Medicine. Boston, Little Brown & Company, 1974*

This is a very readable text, especially for someone new to statistics and unfamiliar with basic concepts and vocabulary. The first part of the book concerns descriptive statistics and probability. The second part contains the principles and methods of statistical inference—that is, drawing conclusions about general populations by studying samples from these populations. This section contains discussions of sequential analysis and longitudinal studies, two topics not generally found in introductory statistical texts, but useful to readers of biomedical articles. The third section of the book, "Statistics in Medical Research," covers

practical issues in the use of biostatistics, including clinical trials, medical surveys and common fallacies in numerical reasoning, and there is an excellent chapter on the critical appraisal of a medical report. Examples are given throughout the book using actual data from current articles; often the author uses these cited studies to point out the misapplication of statistical techniques or misinterpretation of the results.

3. *Hill AB: A Short Textbook of Medical Statistics, 10th Ed. Philadelphia, JB Lippincott, 1977*

The first edition of this book was published in 1937 under the title *Principles of Medical Statistics* and is a classic. Sir Austin Bradford Hill has deliberately left in much of the arithmetic he originally used to illustrate the development and application of each statistical method, with the idea that if researchers are to use a statistical method intelligently, they need to understand the ideas underlying the method and a knowledge of the basic arithmetic is necessary for such understanding. The book was written originally to encourage physicians to become familiar with statistical ideas and elementary methods so that they might have a "hand in the business" of evaluating their research data and published medical articles and books. In addition to the material covered in most introductory statistics texts, the book contains important chapters on clinical trials and common fallacies in medical statistics.

4. *Swinscow TDV: Statistics at Square One. London, British Medical Association, 1978*

In this little (80 pages) book is collected a popular series of articles on simple statistical methods originally published in the *British Medical Journal*. The author says that investigators who can analyze their own data will have a much better understanding of the results and will be able to differentiate more clearly between statistical versus clinical significance. Because complicated statistical methods are rarely necessary in the analysis of many medical and biological problems if the study itself has been well thought out and carefully designed, the methods presented in the book should cover most situations. The examples are drawn mainly from clinical medicine. This book is especially useful as a painless introduction to the world of statistical calculations. The book's main limitation is its focus on the mechanics of statistical computations with little attention to issues of study design and bias.

5. *Gore SM, Altman DG: Statistics in Practice. Devonshire, United Kingdom, Torquay, 1982*

This short volume is a compendium of the articles in the series "Statistics and ethics in medical research" and "Statistics in question" described earlier.

6. *Dunn OJ: Basic Statistics: A Primer for the Biomedical Sciences, 2nd Ed. New York, Wiley & Sons, 1977*

This book is shorter than many introductory texts, as the author wanted to present only a few of the topics in descriptive statistics and statistical inference. One unusual aspect of the book is its emphasis on confidence intervals and the presentation of confidence intervals before hypothesis testing. Dunn clarifies the differences between populations and samples and how one gains information on populations using samples. The major topics covered are simple descriptive statistics, estimation of means and proportions, the x^2 test, correlation and simple linear regression. Examples are drawn from biomedical data and problems are included at the end of each chapter.

7. *Brown BW Jr, Hollander N: Statistics: A Biomedical Introduction. New York, Wiley & Sons, 1977*

Brown and Hollander call their book "a biomedical introduction" because the chapters focus on actual studies from the biomedical sciences. In each chapter statistical procedures are introduced and then these techniques are applied to findings from an actual study. In addition, the authors discuss the motivation behind the development and use of the methods, provide computational lists and illustrate other situations in which a given statistical method can be applied. The topics covered are the same as those found in most introductory statistics books, with the addition of two chapters not usually found in such texts, one on "Surveys and experiments in medical research" and another on "Methods for censored data," which discusses survival analysis when cases are lost to follow-up. Problems are provided.

8. *Zar JH: Biostatistical Analysis. Englewood Cliffs, NJ, Prentice-Hall, 1977*

Zar presents a wide variety of statistical procedures for analyzing data collected in biomedical research. Many relatively advanced topics are covered, including analysis of variance, multiple comparisons and nonparametric methods. The book contains excellent examples worked out in sufficient detail to make it easy for readers to apply the methods to their own data. The only significant omission is the lack of discussion of survival methods and clinical trials. The book's strength is its treatment of statistical computations; it devotes relatively little attention to more qualitative issues of study design and interpretation. There is an extensive set of statistical tables, making this book an excellent reference source for biomedical researchers for most of the methods they will need to apply in their own research.

9. *Feinstein AR: Clinical Biostatistics. St Louis, CV Mosby, 1977*

This volume comprises the best of Feinstein's early essays in the "Clinical biostatistics" series discussed above. The essays are unchanged, but have been reordered to provide a more rational development of ideas than the order in which they were first published.

10. *Wonnacott TH, Wonnacott RJ: Introductory Statistics, 3rd Ed. New York, Wiley & Sons, 1977*

This text covers most of the material on mathematical statistics using college algebra rather than calculus. The authors attempt to show the logical relation between topics that are often covered as isolated sub-

jects in the more elementary nonmathematical introductory texts, such as the relationship between the *t* test and the *F* (variance ratio) test and the relationship between analysis of variance and regression with dummy variables. They have a unique way of illustrating statistical concepts and techniques by using example problems that are worked out in a comprehensive step-by-step fashion. Points that the authors feel are important for a student to retain are set off in boxes and figures and tables are used more effectively than in most introductory statistics texts. Problem sets involve both theory and applications. In addition to the traditional introductory material, the book contains chapters on maximum likelihood estimation, Bayesian inference and Bayesian decision theory.

11. *Dixon WJ, Massey FJ: Introduction to Statistical Analysis, 3rd Ed. New York, McGraw-Hill, 1969*

This introductory book on statistics could be used as a textbook for a year-long introductory course for students from any field in which statistical methods are used. The authors intend that interested students will take further courses with special applications to their own fields after completing the introductory sequence based on this text. Consequently, examples and problem sets are not confined to biomedical research.

Most sections of the book provide a general explanation of the topic followed by a specific worked example. This approach permits readers to follow each step of the process from the statement of the null (and alternate) hypotheses to computation of the appropriate test statistic to interpretation of the results. Presented throughout the book are computational formulas that are to be used in working the extensive problem sets so that readers develop an understanding of where the numbers come from and how sample estimates and test statistics are actually calculated. The book contains an unusually extensive section of statistical tables. All topics are covered thoroughly and—in addition to the more traditional subjects in the areas of descriptive statistics and statistical inference—the book contains chapters on analysis of covariance, advanced topics in analysis of variance, nonparametric statistics and ways of testing for transformations to normality. It is unusual to find so many advanced topics treated in an introductory text that has no rigorous mathematical prerequisite.

12. *Armitage P: Statistical Methods in Medical Research. Oxford, Blackwell Scientific Publisher, 1971*

This introductory book on statistics is intended both for medical research workers with very little mathematical expertise and for professional statisticians who are interested in medical applications of statistics. The emphasis of the book is on the general concepts underlying statistical methods, the purposes for which these methods are designed and the practical steps involved in using these statistical techniques. The author contends that research workers in "quantitative medicine" will be called on more and more to analyze their own data with standard methods. One of the aims of this book is to extend the range of statistical techniques that research workers can confidently apply. The examples come almost entirely from medical research projects. There are no problem sets in the text. (A companion to this book, *Statistical Exercises in Medical Research* by J. F. Osborn, Wiley & Sons, New York, 1979, is a short paperback composed entirely of problem sets and answers keyed to the chapters in this book.)

Armitage's choice of statistical topics reflects his own view of the extent of their usage in medical research. In addition to the more traditional introductory material, subjects covered in this book that would not usually be found in standard texts include vital statistics, sequential analysis and statistical methods in epidemiology and biological assay. Although written for nonmathematicians, this book is more mathematical than others directed at a similar audience, but the coverage of topics is also more complete.

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A Visit With a *Curandero*

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One author visited a Mexican-American folk healer in the Los Angeles area, not as a patient but as a fellow health professional. Information was obtained from this healer, a curandero, *regarding his background, his clientele, the illnesses he treats, the therapeutic techniques he uses and his relationship with the official health care system. This information was generally consistent with statements about* curanderismo *that have appeared in the social sciences literature. It also provided additional insight into practices that have been alluded to in that literature but not described in detail. With few exceptions,* curanderos *would seem to be talented healers whose efforts often benefit their patients and whose continued popularity has important implications for physicians, especially those serving large numbers of people of Mexican descent.*

Curanderos (professional folk healers) are widely patronized in the low-income Mexican-American neighborhoods of southern California. By one estimate, there are 1,000 such healers practicing in Orange County alone (D. Ferrell, "Medicine and magic," *The* [Santa Ana, Calif] *Register,* March 1983, vol 27, pp J1-J4). In Santa Ana, which is the county seat, the site of a University of California Irvine clinic and the home of about 90,000 people of Mexican descent, it is not unusual to see 15 to 20 cars parked in front of a *curandero*'s house as early as 8 AM. A photograph of a Santa Ana healer is prominently featured in a recent *National Geographic* article on Mexican-Americans.[1]

To investigate the reasons for the continuing popularity of *curanderismo* in our area, one of us (J.D.M.) visited a *curandero* in a small city adjacent to Santa Ana—not in the guise of a patient, but as a fellow health professional. As may be imagined, it was not easy to find a folk healer who would talk candidly with a physician but, finally, after considerable delays and difficulties, a meeting was arranged by a Mexican-American nursing assistant from the Santa Ana clinic. This nursing assistant, whom we will call Lupe, had been treated by the *curandero* in question for many years. She was present during the visit.

In the first-person account that follows, pseudonyms have been used and certain minor details have been changed to preserve the anonymity of the participants.

Interview With Mr Flores

Mr Miguel Flores seemed somewhat ill at ease as Lupe and I greeted him in the front yard of his modest but meticulously cared-for home located only a few miles from the luxury condominiums lining the California coast. However, after I presented him with a gift—a plant because Lupe had told me that he loved to garden—he brightened and seemed to relax. We conversed comfortably for a few minutes and then he introduced me to his wife, a pleasant middle-aged woman who spoke only Spanish. She stayed outside, watering plants, as Mr Flores led us toward his office.

My initial impression was of a very intelligent, very sensitive man who looked to be a vigorous 60 years of age and who resembled the late Pablo Casals. He was fluent in English as well as in Spanish, and he spoke with such authority and power that I was reminded of some of the more charismatic priests and physicians I had encountered during my lifetime. His attire, however, was unremarkable, consisting of a short-sleeved shirt and trousers in subdued colors.

The door leading into Mr Flores's office area was separate from the entry to the main quarters. Immediately inside this door was a long corridor lined with enough well-worn chairs to accommodate 20 or more people. There were no patients waiting on this day because it was Mr Flores's day off. Adjoining the waiting

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area was a bathroom, and at the far end of the corridor a door led to his inner office.

This office was at first glance similar to that of any small-town family physician. Mr Flores's bookshelves held a complete set of medical reference books, including a large anatomy text. A 2-foot-high synthetic skeleton was suspended from a hanger on his desk, and an examining table was unobtrusively positioned against a wall. Prominently located above this table was a picture of an old-time family doctor holding the wrist of a bedridden patient as if taking a pulse.

This picture had one remarkable feature, however. Next to the physician stood the figure of Jesus Christ in a white robe, *also* stooped over the patient, *also* showing concern and clearly in partnership with the doctor. Behind Mr Flores's desk were several other rather large religious pictures of a more conventional nature. One showed Christ on the cross, another depicted the Last Supper, and still another portrayed God looking down from Heaven on a seascape.

In several respects, the office had a relaxed, homelike atmosphere. A large red Mexican sombrero hung in the corner—not an ordinary sombrero, but a very ornate one, elaborately decorated with gold trim. Mr Flores's guitar hung on a wall nearby. Opposite his desk was a long studio couch flanked by two easy chairs. Thus, except for the paintings on religious subjects, the office could have been that of virtually any family doctor who practiced out of his home.

At my request, Mr Flores described how he had gotten into the health care business. He had been born in Mexico but his parents, who were agricultural workers, had moved to a farm in New Mexico when he was still quite young. He had spent his early years working as a farm laborer at his parents' side. He was the oldest child in the family and said he had always felt that he was his parents' favorite.

The turning point in Mr Flores's life came when he became seriously ill with an intestinal malady at the age of 20. He had abdominal pain, unremitting diarrhea and weakness in his legs. He consulted a doctor, but even after numerous blood tests and x-ray studies, no diagnosis could be made and nothing could be done to make him feel better. He remained ill for two weeks and was ultimately bedridden.

At that point his mother in desperation summoned the local *curandero* for aid. After massaging his abdomen and legs, the *curandero* gave him some castor oil and prescribed honey and herbal tea to follow. Mr Flores said that his diarrhea increased and he suddenly evacuated something that he believed had plugged up his intestine: a piece of cheese that he had eaten without his parents' knowledge. He felt better almost immediately and progressed through soups and other light foods to a normal diet the next day.

As a result of this experience, Mr Flores became convinced that traditional folk medicine had something to offer people and, with his parents' encouragement, he began to study various folk treatments. First he went to California to enroll in a month-long course in physiotherapy, where he learned a great deal about massage. Afterward he returned to New Mexico and worked with older Mexican-American folk healers as an apprentice. One of his most important mentors was an elderly woman known as a *partera* (midwife) who taught him how to treat female complaints such as menstrual cramps and prolapsed uterus. Treatment of the latter has now become one of his specialties.

About 30 years ago, Mr Flores moved to southern California and has been practicing as a *curandero* in the same location ever since. His clientele is made up of Mexican-American people from all walks of life, including attorneys, schoolteachers and nurses, and he occasionally sees patients who are not of Hispanic descent. He said that he is known along the route to his hometown in Mexico, and that when he goes there to visit, he always has a busy practice—not only in his hometown, but also in places where he stops over on the way. He added that he is often very tired from working so hard, but he loves to help people and feels that he must continue helping them for as long as they need him.

During our visit, Mr Flores repeatedly stressed his concern that he was getting older and there was no one in the neighborhood to replace him. He said that he hoped I would learn some of his skills and use them so that people could get that kind of medical help after he himself had died. He seemed especially worried about his long-term patients who came in for regular treatments. I said that because of my other responsibilities, I would have limited ability to take over his practice even if I acquired his skills, but that I was interested in learning as much as I could and that I would never forget what he told me. He then offered to describe some of his therapeutic methods.

Mr Flores began by discussing the treatment of *empacho,* a well-known Mexican folk illness in which a piece of food (usually something sticky such as cheese or unbaked dough) is thought to block the intestine, become moldy and cause severe abdominal pain. He said that he massages the abdomen from the top down to break up the obstructive mass and administers castor oil to clean out the intestine. He prescribes a regimen of tea and other clear liquids for a day or two, to be followed by a gradual return to a soft diet and then to solid foods. He said that he sees many cases of *empacho* both in children and in adults, and that they almost invariably respond well to this treatment.

At my request, he demonstrated his way of treating *empacho*. Asking me to lie down on my back on the examining table, he pulled up my shirt and unbuckled my pants like any busy, experienced physician wanting to get at the heart of things and began to massage my upper abdomen firmly with both his thumbs. He then pressed on the epigastric region with his fingers, gradually moving them down toward the lower part of the abdomen as if trying to force out an offending food mass. This pushing motion was repeated over and over

with very firm pressure, so that I felt I was getting an extremely vigorous massage.

Mr Flores then asked me to take off my shoes and turn over on my abdomen. He began rubbing the calves of my legs with a similar top-to-bottom motion, saying that this also helped to relax the stomach muscles and cure *empacho,* though he did not know why. Next he massaged my feet so vigorously that he made some of the joints crack. I felt that this massage of my feet and calves did in fact make me relax all over and that my abdominal muscles were probably relaxing along with everything else.

Finally Mr Flores pressed so firmly along the length of my spine that I was worried that something might become dislocated. After moving his hands down my spine from head to coccyx, he repeatedly pulled up the skin over the lumbosacral area, twisted it and let it snap back. He said that this maneuver could be painful—and indeed I found it rather uncomfortable—but that it frequently produced an internal "snapping" that somehow relieved the intestinal obstruction associated with *empacho.*

Following this demonstration, Mr Flores said that he would show me his treatment for tension headache. He had me lie flat on my back and rotated my head from side to side. Suddenly, without warning, he pulled my head to one side and there was a loud popping or snapping of something in my neck. It was not painful, but it was dramatic and slightly frightening. He again rocked my head from side to side and made a similar unexpected movement to the opposite side, and again something inside my neck popped. At the moment of the second popping I felt a distinct sensation of warmth over the lower part of my body—particularly around my feet but also around my abdomen. Shortly after I noticed this, Mr Flores said that I would soon begin to feel some warmth in my body, and that a bit of perspiration would come. He said this was beneficial to headache sufferers and helped to cleanse their bodies of the malady.

Following this impressive experience, I put my shoes on and buttoned myself up and we began to talk about other kinds of treatment that Mr Flores provided. Lupe reminded him that he had treated her daughter for *mal de ojo* (literally, "the sickness that comes from the eye") when the child was feverish and irritable. This folk illness, also called *mal ojo* or simply *ojo,* is thought to be caused—often unintentionally—when one person looks at another in a desirous way. Attractive children who are gazed at by admiring adults are believed to be at risk unless touched prophylactically. Initially Mr Flores seemed reluctant to discuss the subject, but when he saw my interest he became enthusiastic.

He said that he treated *mal de ojo* by passing an uncooked egg over a patient's body three times in the pattern of a cross and then breaking the egg into a glass of water. There, a small black eyelike shape might appear in the yolk; or the yolk might appear to be "cooked"; or it might swirl around as if impelled by a spirit or even pop out of the water about a half inch or so before it settled down. Mr Flores said that any of these phenomena would confirm the diagnosis of *mal de ojo.* He added that if the treatment were successful, one could pass another egg over the patient's body, break it into water and the egg yolk would look perfectly normal, indicating that the harmful spirits had been removed.

Mr Flores told us that prayer was an extremely important feature of his treatment programs. As an example, while he was treating a patient with the egg therapy, he would frequently line up the family members on the couch in his office and pray for them all. Or, if the family was very large, he would bring the whole group into his altar room for mass prayer sessions. He escorted us into this room, which adjoined his office though I had not noticed it as we entered. It contained about 20 chairs and was lit only by a candle burning at one end, so that we had the sensation of looking into a darkened church. At the far end of the room I could discern a cross with rosary beads draped around it, an altar on which a Bible had been placed and religious pictures on the wall behind the altar.

As we walked back into his office, Mr Flores emphasized that the secret of the success of his treatments was the strength of a patient's faith in God and in himself as a healer. He also said that it was just as important for patients to have faith in their physicians as it was for them to have faith in him, and that when patients came to see him after consulting a physician, which frequently happened, he invariably encouraged them to have faith in their physician. He added that he often referred patients to physicians when he felt that they had appendicitis or some other condition that might not respond to his own form of therapy.

I asked Mr Flores whether he always treated patients with their families in the room. He answered that it depended on whether the family members appeared supportive or angry with the patient. If they were angry, he asked them to remain outside. If they were supportive, he kept them near the patient during the treatment and prayed with them all as a group at the end of a session.

He repeatedly emphasized that though he was the agent, it was in fact God who was healing the patients through him. And at one point he made a very interesting statement. In describing one case, he said, "I knew that I had to help that patient and I had to have God come down right then and help him." For a brief moment, I had a glimpse of his belief that he not only had God as his partner in the healing process but also had the power to summon God for help when necessary.

It was clear that Mr Flores believed passionately that he was serving humanity with his work. He described one case in which a patient had consulted him but had failed to follow his advice for the treatment of *empacho.* Instead, the man had gone to a surgeon who had operated on his stomach. When he continued to

have pain after the operation, he returned to Mr Flores, who was afraid to massage him because of the fresh surgical incision and encouraged him to go back to the surgeon instead. The man died a week later and Mr Flores had felt guilty ever since for depriving him of help that might have prevented his death.

A tremendous faith in his own therapeutic powers radiated from Mr Flores as he talked. It was apparent that his personal magnetism, combined with his references to the Lord, his prayers involving the family and his ritualistic techniques, created a healing ambience that was very powerful indeed. While practitioners of scientific medicine still lack a good explanation for the placebo effect, most respect it. And so, in Mr Flores's office, I recalled the words of Dr Kenneth Tittle—a dedicated family physician in Calexico, California—that "We must be prepared to learn more than we can understand" ("Medicine in the Mexican-American Community" [Family Medicine Grand Rounds], Santa Ana, Calif, June 27, 1979).

During our conversation, it became obvious that many people were seeking Mr Flores's help even though it was his day off. He was answering telephone calls from patients every 15 to 20 minutes and in most cases agreed to see them later that day. He told us that one such caller had periodic difficulties with a prolapsed uterus and I asked him how he treated that disorder. He answered that he puts the patient on the examining table in a position that is rather like the one assumed for sigmoidoscopy: chest down and buttocks elevated in the air. He then massages the patient's abdomen from the pubis toward the epigastrium. He remarked that this motion, combined with the position of the body, helps the uterus fall back into place where it belongs, adding that he had treated many prolapsed uteruses in this way and that most had stayed fixed and painfree for long periods. He was also proud of the fact that his method did not require the patient to disrobe or submit to a pelvic examination.

Mr Flores repeatedly cautioned me that one had to be careful about discussing such therapies with people other than patients. He said that some would be skeptical and laugh and that others might make legal difficulties. I noticed that even with me, Mr Flores shied away from answering questions about herbal remedies; he was clearly avoiding the subject. Finally, however, when Lupe mentioned several herbs that had been helpful in her family—*yerba buena* (mint) and *manzanilla* (camomile) for *empacho,* cornsilk for urinary tract infection and *ruda* (rue) for a pain in the ear—he admitted that he was familiar with all of them. He then confided that though he was reluctant to prescribe herbal remedies unless he knew the patient very well, he did in fact have them at his disposal. He said that most could be obtained from a pharmaceutic supply house in Utah in capsule form, and that the capsules were effective because people believed in them.

Mr Flores then told a story that explained why he was at first reluctant to discuss his use of herbs. For many years he had been afraid that the health authorities would come and close down his operation because he was practicing medicine without a license. One day the knock on the door finally came. A city official appeared, remarked that sick people had been observed visiting his home and asked him whether he was providing some kind of health care. Mr Flores responded that he prayed for people and tried to help them feel better but that he was not practicing as a physician. However, the official told him that he would have to have some kind of license in order to continue his business.

Panic-stricken, Mr Flores called a patient of his who was an attorney. The attorney told him that he would look into the matter, and several days later he reported that Mr Flores had nothing to worry about—he was now licensed as a health practitioner. He then presented Mr Flores with a certificate signed by a city clerk stating that he was indeed a licensed "Christian Health Healer." Mr Flores proudly showed me this diploma-like certificate, which was prominently displayed on his office wall. He also confided that even though he tries to discourage them from doing so, most of his patients call him "doctor."

As we were about to leave, still another patient telephoned complaining of a prolapsed uterus. Apparently she was fairly acculturated, for Mr Flores spoke to her in English, and she could be heard speaking excitedly in English at the other end of the line. After hanging up the receiver, he told us that she had emotional problems, that she needed help and that he was going to provide it. He spoke with such quiet conviction that there was no doubt in our minds that his efforts were going to help her.

Mr Flores and I then exchanged phone numbers and agreed to meet again, either at the Santa Ana clinic or at his home. With that, Lupe and I left, exiting from the chapel-like darkness of his office into the brilliant southern California sunshine.

Discussion

The encounter described above illustrates several important features of *curanderismo* as it exists in the Los Angeles area today, including the illnesses treated by *curanderos,* the therapeutic techniques used, the way in which healers are trained, the economic viability of *curanderismo* and the relation between *curanderos* and the official health care system. Other accounts of encounters with *curanderos,* mostly very brief, are scattered throughout the social science literature.[2-14] In general, the information provided by Mr Flores is consistent with such accounts; both his remarks and published sources are drawn on in the following discussion.

Illnesses Treated by Curanderos

Today, most *curanderos* limit their practices to an array of folk illnesses—such as the *empacho* and *mal de ojo* treated by Mr Flores—plus certain stubborn or chronic conditions such as impotence, infertility, headaches, fatigue and asthma that frequently have an

emotional component. This is not to say that patients may not have physical ailments, for they often do, and a *curandero* treats them with physical means such as massage and herbs. But even in such cases, both healer and patient are usually aware that psychologic factors may be involved. In short, the mind-body dichotomy characterizing the biomedical model of illness is largely absent from *curanderismo*.[3,14,15]

Of 100 Mexican-born clinic patients whom we interviewed in Santa Ana in 1980, there were 17 who said they had visited a *curandero* at some time in their lives and an additional 33 said that someone in their family had done so. The reasons given for the last consultation show this lack of a mind-body distinction. Of 50 consultations, 21 were for *mal puesto* (bewitchment, often manifest in somatic symptoms; literally, "an evil put on"), 8 were for *susto* (fright sickness), 4 were for *empacho,* 2 were for chest pain, 2 were for help in finding a missing relative and the remaining 13 were for a variety of complaints including deafness, twisted foot, alcoholism, irregular menses, infertility, marital problems, measles, diarrhea and *nervios* ("nerves").

It is evident from this list that *curanderos* are thought to have an extraordinarily wide range of powers. Many do possess a good deal of solid medical knowledge, though it is likely to be spotty and fragmented. Usually they are able to recognize conditions such as fractures that transcend their sphere of competence, and in such cases—perhaps partly out of concern for their reputation—will advise patients to seek scientific medical care.[4,11] (In fact, they themselves go to physicians at times.[12,14,16,17])

Therapeutic Techniques

A *curandero* relies on an ancient system of folk medicine that originated in the Americas and reflects both Spanish and Indian influences.[18] Today the latter is evident primarily in the extensive medicinal use of native herbs, whereas the influence of Spain—and specifically of Roman Catholicism—is much more visible. For example, ritual prayers in a setting filled with religious appurtenances such as crucifixes, images of the Virgin of Guadalupe, holy water and candles are of central importance. In addition, *curanderos* usually see themselves, and are seen by others, as having a special healing gift *(don)* given by God—in fact, this is what distinguishes them from other types of folk healers—and as performing a kind of spiritual function in the service of God.[5,6,17,19] And most *curanderos* are thought to be able to remove hexes *(mal puestos)* that have been put on a victim by a witch in league with the Devil.[11]

A typical *curandero* also makes use of what might be called "white magic"—procedures that are not tied directly to the Church but rather appear to be rooted in Spanish folk medicine or Indian ritual. Massage is one example. Another is the extensive use of raw eggs both for diagnosis and for treatment. Frequently, as in Mr Flores's *mal de ojo* therapy, an egg is broken into a dish and is found to show unusual configurations or to contain foreign material, indicating that a patient's illness has been intentionally or unintentionally caused by another person.

But traditional therapies such as these represent only a small part of the armamentarium of modern *curanderos*. Most have adopted at least some of the techniques and tools of physicians. Like Mr Flores, many furnish their offices with scientific trappings such as medical texts and plastic models of the human skeleton. And as early as 1964, one investigator observed it was "becoming quite common for *curanderos* to give their patients written prescriptions for herb medicine. . . . A few *curanderos* give injections of vitamins or penicillin."[4] (Such injectables are easily available in Mexico, and they are—as we have noted elsewhere—highly esteemed for their supposedly rapid results.[20])

Still other important therapeutic tools used by *curanderos* are those of reassurance and suggestion.[9] Typically a *curandero* is a charismatic, highly respected person who projects great personal concern for patients and their families *(personalismo)* and a firm belief in the efficacy of the treatments, both of which are undoubtedly conducive to patients' sense of well-being and possibly to healing as well. As one observer has put it, "The folk curer nearly always succeeds because, even though disease symptoms may continue, he knows how to make his patient feel better."[21] The very setting in which such a curer practices—a private home—is reassuring because of its familiarity.[16]

Far from treating a disease in isolation, or even a patient in isolation, *curanderos* usually deal with a patient in context—that is, in relation to others in both family and community. In the process of diagnosis, for example, they are likely to inquire about the nature of a patient's recent interpersonal contacts. Furthermore, if a patient's friends and relatives appear supportive rather than angry, they often involve them in the healing session itself. And *curanderos* emphasize the need for a patient to have absolute faith in God, in the *curandero* and in the treatment process. (We remember Mr Flores's insistence on excluding negative elements from the therapeutic setting.) Strategies such as these would appear to have important implications for physicians.

As one would expect, *curanderos* show a good deal of variation in personal style and therapeutic technique.[22] They are less diverse than they might at first seem, however. Part of the problem is terminology. In the social sciences literature, the word *curandero* has often been used quite loosely to refer to any or all of the following: a witch, a neighborhood woman who knows a bit about healing, a spiritualist, a specialist in massage and a herbalist. Most serious students of *curanderismo* prefer to reserve the term for full-time professional healers who use their exceptional spiritual powers to treat a broad range of ailments, including those thought to be caused by witchcraft. Lesser, or more specialized, healers are best referred to by a different name. In reality, the basic tools of a *curandero*—herbs, prayer, massage, reassurance and sug-

gestion—are common to *curanderismo* as it is practiced in many different regions.[9,14]

Training a Curandero

As noted above, the *curanderos'* power to heal—their *don*—is thought to be given by God. In some cases, the *don* is given after they themselves, or members of their families, recover from a grave illness.[4] In other cases, they are born with the gift of healing, frequently inheriting it from a parent or grandparent.[17] Though most *curanderos* are adults, in rare instances a child—such as the famous Niño Fidencio—may gain recognition as an effective curer.[4,5,13,14] Like Mr Flores, most *curanderos* learn their actual healing techniques through apprenticeship. No special ordeals or initiations are required, and both men and women may be healers (female = *curandera*). Almost always they are extremely religious people.[6]

Economic Viability of Curanderismo *as a Profession*

Curanderos may be supported entirely by donations or they may make an agreement—tacit or explicit—that they will be paid only if the patient gets well. Almost never is there a set fee for services.[6,16,18] This overt espousal of poverty is consistent with the religious orientation of *curanderismo*. In fact, however, successful *curanderos* do quite well financially by virtue of the gifts they receive from their large clienteles.[11] We recall that for more than 30 years, Mr Flores has been able to make a living solely from such donations.

Although some healers engage in marginal practices such as selling candles and icons, *curanderos* are generally seen as more altruistic than physicians.[4,5] In most cases, they are less expensive for patients. A typical "suggested donation" in southern California is $5 to $10 per visit, the lower amount being charged if a client is a long-time customer. Importantly, *curanderos* rarely initiate discussion of payment; rather, they wait until a patient broaches the subject at the end of a treatment session. One can readily see the contrast between such personalized transactions and the impersonal payment process characteristic of most US health care facilities.

Because most sick people get well regardless of what is done for them, it is relatively easy for charismatic persons such as Mr Flores to build up a devoted clientele. Even when a folk cure fails, the failure may be ignored, blamed on a patient's having waited too long before seeking help or attributed to noncompliance with the therapy. In addition, many believe that if a *curandero* is unable to cure a patient, the failure is due to God's will: the curer is exonerated.[4,6,23] The efforts of a *curandero*—unlike those of a physician—are almost never openly criticized, at least by those who patronize such healers. People may change to another *curandero* if their medical problems are not alleviated, but (possibly out of fear of magical retribution) they rarely voice dissatisfaction with the initial therapy or refuse to pay for it. Thus, many factors unite to make *curanderismo* a viable profession in southern California today.

Curanderos *and the Official Health Care System*

Still, there is abundant evidence that *curanderos* are apprehensive about their relations with physicians and with the law. We remember, for example, that Mr Flores chose to begin by discussing *empacho,* perhaps the least mystical of the folk disorders. However, he was rather reluctant to talk about *mal de ojo* and did not raise the subject of *mal puesto,* though Lupe said later that he was able to cure it by a cleansing rite involving "sweeping" a patient with branches from a special tree. In short, it seems clear that he did not want to undermine his credibility by discussing ailments that physicians might view as having to do with the supernatural.

We remember also that at no time did Mr Flores refer to himself or to any other folk healer as a *curandero.* It is possible that the word *curandero* is not used because it is too general (analogous to the English word *curer*). In southern California, and reportedly in Arizona as well,[12] people who cure have many different specialties that are often mentioned instead—prolapsed uterus in the case of Mr Flores, for example. In addition, however, the word *curandero* has pejorative overtones in the United States and in the urban centers of Mexico, even though a substantial part of the Mexican population reportedly still has access only to traditional healers.[24] Virtually all Spanish-English dictionaries gloss the word as "quack curer," and it is not uncommon for people to associate *curanderismo* with witchcraft.[4,25,26]

Some *curanderos* are in fact frank charlatans. Others are misguided persons who mean well but can cause great harm because of their lack of medical knowledge. In one case known to us, a baby with a disorder of the gastrointestinal tract folk-diagnosed as *empacho* almost died after being given an oral dose of liquid mercury by a *curandera.* The history is instructive: the baby was being cared for by his grandmother, who had first sought medical care at a clinic but had turned to a *curandera* after receiving what she considered to be inadequate personal attention and perfunctory treatment. The *curandera* was arrested and ordered to close her practice.

Incidents such as these point up the danger inherent in *curanderismo:* a patient may seek relief from a folk healer even when scientific medical treatment is urgently indicated, and for one reason or another a healer may not refer the patient to a physician. We have seen cases of pelvic inflammatory disease and even appendicitis that had worsened while a patient was being treated for *empacho.* It is not surprising, then, that the relation between the *curandero* and the official health care system is likely to be strained at best, and that the medical practices acts of many states are written in such a way as to make *curanderismo* potentially against the law.[14] Indeed, this is one of the main reasons that

we lack reliable data on the number of *curanderos* in the country as a whole.

Income, Education and Adherence to Curanderismo

We also lack reliable data on the prevalence of *curandero* use among various segments of the Mexican-American population. On the one hand, in seven major studies carried out between 1966 and 1980,[26-32] a small but substantial number of persons reported the use of *curanderos* (the mean percentage was 24%, with the range being 2% to 70%). Our own research tends to confirm this finding; as noted above, 17% of 100 Mexican-born clinic patients said that they had visited a *curandero*.

On the other hand, it is crucial to remember that most of the data, including our own, were gathered from the least affluent, least educated and least acculturated group of people of Mexican descent. Data for other groups are badly needed. Although most Mexican-Americans are at the lower end of the socioeconomic scale, it is hazardous to make generalizations about health care behavior based on studies of predominantly low-income families, as has been pointed out in an important review article.[33] Those interested in *curanderismo* should be aware that the subject is a sensitive one among many United States-born people of Mexican descent, especially if they have been personally traumatized by harmful stereotypes.

Considerable evidence exists that only a minority of Mexican-Americans patronize *curanderos,* even this minority patronizes physicians as well[26-30,32,34] and—as one could guess—allegiance to traditional medicine declines with advances in socioeconomic status and, specifically, with advances in educational level.[35] Nevertheless, it is also true that *curanderos,* even though their name may be going out of fashion, continue to thrive in the low-income Mexican-American neighborhoods of the border states of the Southwest.[14,36] Physicians should not feel threatened by these traditional practitioners who, on balance, do much more good than harm. Instead they should heed the lessons to be learned from the persistent popularity of these accessible, low-cost and culturally sensitive health care providers.

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Doctoring in Eastern Europe

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Health care in Eastern Europe has not achieved world standards nor the goals of planners of socialist societies. With luck, perseverance, bribes or good connections, it is possible to obtain good medical and surgical care in Eastern Europe for a major illness. Primary and even secondary care usually are substandard, however, and often completely unacceptable to most Western foreigners. The reasons for this are complex but mainly rooted in different attitudes of health workers towards their patients, poor physical plants, poor salary structures, inadequate advancement opportunities for health care workers, poor social status and professional recognition for nurses and almost complete isolation of the average primary care doctor from hospital medicine.

Two years as Regional Medical Counselor for the US Department of State in Eastern Europe provided an excellent opportunity to gain some insight into medical practices in Yugoslavia, Rumania, Bulgaria, Hungary, Czechoslovakia and, to a lesser extent, the USSR. Encounters with critically ill foreigners at hospitals in these countries demonstrated that good medical care can be obtained, if one is lucky to contact the right facility or has previously established channels of communication with the best professional talent. On the other hand, there was a substantial number of medical horror stories which present a picture of incompetence, lack of interest and plain dehumanizing treatment of patients. Such horror stories may, of course, be collected in most countries. In Eastern Europe, however, they seem to be more common than one might expect in a region that has a history of medical colleges and hospitals dating back several hundred years.

What are some of the reasons for this? Could it be lack of medical manpower? There is no shortage of physicians in Eastern Europe. The number of patients treated daily by an average doctor is well within the acceptable range. Often, however, physicians do work under chaotic circumstances with poor patient flow and virtually no auxiliary support. Well-trained professional nursing staffs are a rarity and this seriously impedes the efficient delivery of health care. One reason for this is the fact that nursing is not considered to be a prestigious occupation. Educational standards for nurses are poor and working conditions dismal, which leave the young working force to prefer employment in factories or offices. Local physicians are aware of this problem, but I have seen little effort on their part to alter it. Nurses are rarely treated as professional colleagues by doctors. This is evident in the general absence of nurses at medical conferences, and in the usual lack of formal participation by nurses during discussions of management problems.

Is Modern Equipment Lacking?

Most major teaching and referral hospitals in the region seem to have essential equipment. Some have outstanding equipment. One university hospital in Belgrade has the latest in x-ray units, yet I was not able to obtain a remotely acceptable gastrointestinal study at the same institution. Equipment is scattered and often not fully utilized, or it is used by persons who have not had the opportunity to develop real expertise in its operation. Maintenance is frequently poor and "downtime" considerable. Medical planning is often tilted to the construction of expensive show projects such as a new army medical center or specialty hospital which serves a relatively small population. Indications for the use of expensive equipment such as computed tomographic scanners are often questionable or of a political nature; a situation expected to be more common in the profit-making environment of a capitalistic society. There is, however, a problem of access to this equipment for average citizens. Outpatient clinics are usually poorly equipped and frighteningly dirty. They are, however, charged with providing

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only basic medical services that could be done with very simple equipment, provided one had a mature and well-motivated staff. It has been my experience that lack of equipment is often used as an excuse for lack of willingness to provide services and use whatever tools are at hand.

Are the Physicians Incompetent?

Medical education in most of Eastern Europe has been shifting from the Austro-Germanic mold of formal lectures with little practical bedside teaching, to a more clinical format resembling the French or Anglo-Saxon approach. Examinations, however, are still almost exclusively oral, infrequent and not very objective. International medical journals and current foreign texts are either not available to students or are extremely expensive. Most medical school libraries in Eastern Europe do subscribe to the major Western medical journals, but it takes a long time to circulate a single copy of a medical periodical through the entire staff of an institution. The situation is better in Yugoslavia where professionals, as do all citizens, enjoy the privilege of unrestricted travel abroad provided they have money. The rather poor performance of all Eastern European medical graduates on the ECFMG (Educational Council for Foreign Medical Graduates) examination, when compared with that of graduates from some developing countries, could suggest inferior basic medical education. Average pass rates of 1978 ECFMG candidates from Czechoslovakia, Hungary, Poland, Rumania, Yugoslavia, Bulgaria and the USSR were 24%. Those for 1978 candidates from Ghana, Kenya, Jamaica, Mexico, Lebanon, Malaysia, Singapore and Thailand were 69%. One must also consider that not necessarily the best foreign medical school graduates are lining up for the ECFMG or VQE (Visa Qualifying Examination) examinations. Most of the brightest young doctors of Eastern Europe will somehow manage to settle down to a local academic career.

To be pitied are the majority of the physicians who work in outpatient clinics (health centers, polyclinics), often have had little teaching hospital experience, are remote from hospital medicine and are overwhelmed by patients with minor complaints who demand a signature on the mandatory sick-leave slips. Most outpatient clinics are housed in decrepit-looking buildings which frequently have been converted from other use and which only rarely have been provided with adequate laboratory or x-ray support. Physicians usually work out of a combined office and examining room where a patient has to undress with the doctor standing by. With a long line of patients waiting outside, it is often easier simply to exchange a few words, unbutton a shirt or blouse and write out a quick prescription rather than examine the patient. Such a clinic doctor has poor professional recognition and less job satisfaction.

Most medical horror stories that have come to my attention have had to do with poor communication, no continuity or coordination of care by different "specialists" and inadequate history-taking and patient examination. Poor follow-up care, overprescribing in lieu of diagnosis and disinterested treatment by physicians are also common complaints.

One of the most irritating problems I have noted throughout Eastern Europe was the almost uniform unwillingness of local physicians to observe unclear clinical findings in a patient for a period of time without massive "shotgun therapy." This often added further symptoms, obscured signs, created anxiety and caused additional delay in diagnosis and specific treatment.

A rather unexpected phenomenon was the government's support of some *quackery* and *charlatanism* that can be found in some Communist states. Examples are the Gerovital Institute in Bucharest and its very dynamic octogenarian director, Dr Ana Aslan. The procaine rejuvenation treatment, combined with conventional medicine practiced at that institution, has become an excellent hard currency earner for Rumania and is heavily advertised abroad. A line of "rejuvenating" cosmetics is also marketed successfully under Ana Aslan's and the Gerovital name. One large eye clinic in Moscow touts an unsubstantiated and, even by most Soviet ophthalmologists, disclaimed vitamin therapy for retinitis pigmentosa. The clinic attracts a substantial number of foreign patients who hope for a cure of this progressive disorder. Some medical practices and medications that have been discarded as ineffective or dangerous in the West have managed to hang on in Eastern Europe. Examples are the widespread routine use of progestational agents for threatened abortion and the common prescribing of chloramphenicol for minor infections.

I have also been impressed by the long-term hospital stays for patients in most of the hospitals I have visited in Eastern Europe. Examples are the average one month admission for children with uncomplicated appendectomies (personal observation, University Hospital, Sofia, Bulgaria) and keeping a young person with simple lobar pneumococcal pneumonia in hospital until all x-ray findings cleared (more than a month in Belgrade University Hospital). It is not uncommon at most city hospitals to see large numbers of patients walking about the grounds looking perfectly fit. Games of soccer can also be observed when the weather is good. It is, on the other hand, frequently very difficult to find a hospital bed for a medical or surgical emergency, and most hospitals will be fully occupied most of the time. These practices must surely be eating up increasingly scarce health care funds.

A distressing feature of hospital care in Eastern Europe is the very limited *access to patients* by family members. In front of hospitals it is common to see people standing outside the gate and shouting up to a patient who hangs out of the hospital window. I have even seen patients lower baskets on strings out of windows for their relatives to fill with fruit, snacks or reading material. This sight is even more common in

front of maternity hospitals, where access to a new mother is severely restricted. Short visiting hours can be rationalized by the fact that private rooms are extremely scarce and most patients are in large 8- to 20-bed wards where a horde of uncontrolled visitors would be very disruptive. This, however, is of little solace to a mother who is unable to visit her sick child other than for a quick glance into a large ward through a glass partition.

General Dissatisfaction With Medical Services

I have observed that unhappiness with medical services is freely expressed by local citizens and foreign residents throughout Eastern Europe. In Western countries, lay criticism seems mainly directed at regional scarcity of services and their cost. Eastern European complaints are different. Local citizens and most resident foreigners will admit that some form of care is readily available to all in the Communist world. They do, however, feel that it is very often rendered arrogantly and impersonally. Problems are tackled without adequate history or examination, and the local public recognizes that a quick prescription or injection usually takes the place of logical evaluation and well-planned treatment. A request from a patient for an explanation of a diagnosis and therapy is frequently viewed as an insult by physicians, who are unaccustomed to being questioned. Access to secondary or tertiary care is limited. *Bribes* in the form of a "blue envelope" (Yugoslavia) or *pod stolem,* "under the table" (USSR), are almost the norm. This does not include gifts to the nursing staff to insure adequate care postoperatively. Emergency care including major operations will, of course, be rendered without such gifts, but rarely by the "first team." Elective procedures all have very long waiting lists, which can be avoided by an appropriate gift or a friend in a high place.

There are occasional drastic shortages of drugs throughout the Soviet Union and its satellites. They are less frequent, but not unknown, in Yugoslavia where, for example, x-ray film became virtually unobtainable for a period early in 1980. Basic medications such as penicillin have, at times, become unavailable in pharmacies in the USSR. I know of one episode when insulin was very difficult to procure in Bulgaria. When all this is seen in a setting where the population has been promised "free" care for all their medical and dental needs, and is charged up to 70% of their modest salary in taxes and social security deductions (Yugoslavia), it is easy to understand the growing dissatisfaction of the populace.

On the positive side, it must be noted that a substantial number of ordinary Yugoslav citizens of all social backgrounds are referred abroad every year for specialized medical or surgical care. Heart surgery in the United States (about 1 million dollars worth in 1979), neurosurgery and cancer chemotherapy in Switzerland, renal transplants in France and some specialized orthopedic treatment abroad head the list. The substantial costs for these are borne by the Yugoslav Social Security System, after a board of local specialists rules that this type of treatment is not available locally. Evacuation of high-ranking party officials to Western countries, including the United States, from the Soviet Union and its satellites also is not unknown, but numbers have been small and such events have received little, if any, publicity.

Dental Care

One sees many people with rotting or missing teeth on the streets of any Eastern European city. The physical plants of dental clinics, techniques and materials are crude and decades behind the times. A dentist works usually from one chair and with a shared assistant. There is little understanding of modern concepts of pathophysiology of oral structures and practically no meaningful preventive dentistry. Fillings are poorly placed (often not countersunk) and usually not polished or fitted to the bite. Crowns are made out of either plastic materials or shiny stainless steel (favored in the USSR). Gold is available but beyond the reach of common citizens. City water is not fluorinated, and dental floss is generally unknown and unavailable. Fluoride supplementation of infants' and children's diets is not practiced. There is no porcelain laboratory for the general public in the entire region. A porcelain laboratory had opened in 1979 in Zagreb, Croatia, and was doing a land-office business. Private dental and medical practice was, however, again phased out in Croatia, the only Yugoslav republic where it ever existed officially.

Medical Services Administration

Would more competent medical services administration improve the system? Polyclinic and hospital administration is highly political in all of Eastern Europe. Directors, administrators and chiefs of service are either appointed by the government (usually with Communist party approval) or selected by the self-management committee with party concurrence (Yugoslavia). It is not uncommon under both systems that a political activist with few professional qualifications ends up in the director's position. I know of a situation where an x-ray technician (a poor one at that) sits on the executive committee of a local hospital and thus determines the salary, fringe benefits and working conditions of his supervisor, the radiologist. One must understand that such an executive committee also has authority to assign scarce housing, and therefore exerts great influence on the staff's personal as well as professional lives. Needless to say, it is unlikely that this radiologist will risk offending his influential aide by criticizing the quality of his work.

It is probable that professional and cost-effective medical administration could improve health care delivery in Eastern Europe. Allowing independent private practice in medicine and dentistry could also result in improvements of standards in the public sector. Experience in Croatia and elsewhere in the world (Thailand) has shown that innovations and new cost-effec-

tive techniques are more likely to appear first in the private sector. Private practitioners would also take some of the burden from public clinics and possibly reduce graft and corruption which is demoralizing the entire system. Development of private practice is, however, unlikely to happen soon in Communist Eastern Europe. The concept is an anathema to socialist doctrine.

Foreign Residents and Tourists

Foreigners do not understand the local language well in most instances, nor do the doctors usually understand theirs. Poor communication results in insecurity and leads to misunderstanding. If a foreigner comes from Western Europe, North America or the Far East, he has different expectations from a physician and dentist. The usual Eastern European doctor, on the other hand, does not understand the foreign patient's many questions and often interprets them as insulting and questioning his competence. This, in turn, can create a tense atmosphere and adds little to a comforting doctor-patient relationship. Furthermore, a foreign patient rarely understands the Eastern European health care system. He has not heard about "blue envelopes" or *pod stolem,* which are also not covered by Blue Cross, and he consequently gets the kind of care that the local doctor feels that he deserves. Those countries that have special clinics ("diplomatic clinics") for resident foreigners and tourists present further problems to an expatriate. Since a doctor's financial lot in Communist lands is not a rosy one, he, not being a saint in most instances, will tend to seek a job in a hospital or clinic where "blue envelopes" or *pod stolem* are ample and fairly distributed. An occasional bottle of scotch or carton of American cigarettes presented to him by a thankful foreigner does not make his car run or his wife happy. The "suspicious" and "demanding" foreigners also are more difficult to deal with. Many local doctors, therefore, feel that they are best avoided. This acts as a negative selection factor for jobs in "diplomatic clinics."

Public Health and Preventive Medicine

A great deal of stress has been placed on public health in "East Bloc" countries and Yugoslavia. Immunization programs for children appear to function well and include bacille Calmette-Guérin (BCG) vaccination. The quality and handling of BCG vaccines appear to be, however, somewhat suspect. Many children do not convert their tuberculin reactivity after BCG, and childhood progessive tuberculosis still appears to be common. It is even seen in BCG-vaccinated children, an experience contrary to that of France and other Western countries with long-standing BCG programs. Measles vaccination is not yet comprehensive, and outbreaks of this preventable disease occur. Yugoslavia has, however, lately been giving measles vaccine to most children. A reasonably effective tuberculosis case-finding program, based on microfilming of populations in factories, schools and on the street, can be seen throughout the region. Chest fluoroscopy, however, is still widely practiced in outpatient clinics where x-ray film shortages are not uncommon. Enteric fevers are relatively rare. The incidence of hepatitis is only slightly greater than in North America, and most outbreaks occur in rural areas due to contaminated well water supplies. Giardiasis is a common seasonal problem in the Soviet Union; few long-term foreign residents in Leningrad seem to escape at least one episode. The persistent occurrence of this disease in this large modern city is still denied by Leningrad public health authorities. Rabies is endemic among wild animals throughout continental Europe, but dog control in cities functions very well in the region, and the disease does not pose a threat to urban populations.

There seems to be very little respect for workman's health protection in the Communist world. Driving through the countryside, one is greatly impressed by the many factories spitting black smoke from chimneys and covering entire communities with a thick layer of dirt. I have seen asbestos workers cut boards without respiratory protection. Many other procedures are done in an environment which, in most Western countries, would result in instant closure of the enterprise. Air pollution of cities is an increasing problem due to the use of brown coal. With the high cost of oil and natural gas, little can be done at present to improve this situation which is particularly bad during the winter in Belgrade and Budapest.

Venereal disease (gonorrhea, nonspecific urethritis, genital herpes and syphilis) are not uncommon. Moscow seems to have experienced a small epidemic during 1979 and 1980. Prostitution is not rare in Eastern Europe and in the Soviet Union. Most Warsaw Pact countries have a community of "ladies of the night" who seem to cater exclusively to foreign residents and visitors, presumably with police concurrence. They are particularly visible around the tourist hotels of Prague, Budapest and Bucharest.

A whole chapter can be written about the terrible state of public toilet facilities throughout Eastern Europe. Most require great urgency and rubber boots for safe entry. Serbia is also notorious for pollution of its countryside and city streets by garbage. The author has seen policemen throw soft drink bottles or paper sacks on city streets, and that in full view of the public. The important highway between Zagreb and Belgrade is literally a garbage dump. This probably has little effect on public health but connotes a general apathy and lack of pride in one's country. It seems to carry over into the working place, which often looks equally disorderly. This attitude might also contribute to an increased accident rate, poor work motivation and low productivity. Absentee figures of up to 25% of a factory's work force are not exceptional throughout Eastern Europe.

The deterioration and lack of repair of buildings in the cities of Yugoslavia and Czechoslovakia, in particular, have resulted in a new public health hazard: injuries from falling bricks and stucco. Any recent

visitor to Belgrade, Prague or Zagreb will confirm this hazard. It was first brought to my attention by a local anesthesiologist, and again when I was almost killed by a huge stucco piece crashing about 10 feet from me onto the sidewalk of a major city street in Belgrade.

During two years of travel through Eastern Europe, I have not seen any evidence of a serious anti-smoking campaign. Nonsmoking seats on Warsaw Bloc and Yugoslav airlines are either not designated or the signs are totally ignored.

Hard-drug abuse does not seem to be a serious problem in Eastern Europe. Cannabis is used by a small number of young people in most Balkan countries where it has been known for generations. Alcohol abuse is, however, an admittedly serious problem throughout the region, and the USSR has a highly visible poster campaign dealing with "the evil of drink."

The Future

The general economic difficulties that have befallen the Western world are shared by the Communist East. Work ethic is declining everywhere. Idealism and enthusiasm for social changes are giving place to cynicism and selfishness. The utopia that was promised one or more generations ago has not materialized, and the region is falling behind the West in social, ethical and economic development. Every Warsaw Pact country I have visited seems to have a two-tier consumer economy: the visible one and one that takes place entirely *pod stolem*. Desirable goods and services are sold or rendered only in return for special favors or hard currency, or to close friends and higher officials. This takes place in special stores (for party officials or those with hard currency) or simply by secreting desirable goods behind the counter. Most Soviet bloc countries have special hospitals or special sections of general hospitals strictly reserved for high officials. Most ordinary citizens understand the system and know how to procure better services in polyclinics or general hospitals by paying bribes. The wide distribution of corruption that one finds in Eastern Europe is truly amazing, even to someone who has spent almost two decades in Africa, the Middle East and Southeast Asia. This sad state of affairs does little to instill good work habits or compassion for one's comrades in newly graduated health workers. They either learn cynically how to float with the system, or become bitter and drift along doing a bare minimum.

Priorities seem to be shifting from ambitious social programs to more immediately pressing needs such as the purchase of oil and defense spending. Health care is not likely to receive many added resources in this changing environment.

Medigap: Are We Cheating the Nation's Elderly?

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"You should know your Medicare benefits as well as you know how much money you have in the bank."[1] This comment, made in 1969, typifies the nation's wishful thinking in the early stages of the Medicare program. Unfortunately, it has become clear today that having a thorough knowledge of Medicare benefits is virtually impossible, and that for the elderly to uncover the complexities of the program approaches an exercise in futility.

Since 1965 Medicare has been providing the elderly with some form of assistance in dealing with rising health care costs. Medicare, however, was never designed as a comprehensive program. Instead, it was meant to provide payments primarily for acute, short-term illnesses. As a result, the benefit structure of Medicare is inconsistent and often confusing to the elderly. There exist many gaps in Medicare coverage. This fact has understandably led many older persons to purchase private health insurance for protection in filling these gaps so that the health care needs not funded by Medicare will be covered by some other source. Problems in representation of these Medicare supplement health insurance policies, called Medigap policies, are the main focus of this paper. The Medigap problem involves a segment of the insurance industry which may have exploited the needs and anxieties of the elderly. More than 70% of the nation's Medicare recipients have some form of supplemental insurance, yet it seems that in many instances the elderly may be wasting their money on unnecessary, superfluous private coverage.[1]

As costs for medical care continue to rise sharply, Medicare pays less and less of the total bill. Those over 65 pay much more out of pocket for the medical care today than they did in 1965 when Medicare began. In 1969 Medicare paid for 50% of the total national bill for senior citizens, while by 1980 the total dwindled to 38%.[2] There has been a corresponding increase in the number of seniors who buy private insurance. The United States House of Representatives, at the 95th Congress, concluded that about a fourth of the elderly buy more than one Medigap policy, while some have as many as 30 different policies, most supplying overlapping benefits.[3] They buy out of fear that the cost of an illness will deplete their low incomes and limited assets.[3]

The seniors are often not in the best position to find the most sensible policy to buy among Medigap policies. It is difficult for any consumer, much less a senior citizen, to determine the worth of the product by reading an insurance policy.[4] Both the structure and wording of such drafts are often unclear to an untrained, timid customer, and it is often an effective sales pitch, rather than the facts of the policy, that convinces an older customer to buy. A second factor rests in the psyche of the purchasers. For the most part, when seniors buy an insurance policy it is a "reflex action."[3] Rarely will an elderly person take the time to comparison shop. Because they are motivated by fear and intimidated by the high costs of medical care, they stock up on Medigap policies as if they believe the more they have, the better their health will be and the less they will have to worry. Sadly, the distorted logic "if one is good then two must be better" has led to a tremendous waste of money for older Americans, contributing to the Medigap crisis.

Yet it is the structure and function of Medicare that are partially responsible for there being a Medigap problem in the first place, and with this in mind it becomes clear that any explanation of Medigap abuses must start with a look at Medicare. The federal insurance program consists of two parts. Part A, the hospital insurance component, helps pay for inpatient hospital care. It also covers a limited amount of posthospital convalescence in a skilled nursing facility (SNF) certified by the Medicare program, for some home health care and since 1973 for victims of end-stage renal disease. Of the eligible elderly population 98% are covered by Part A.[4] Part B, supplementary medical insurance, includes physician and ancillary services and assorted nonhospital services. Part B is voluntary, and

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participation requires payment of a small monthly fee. There are 97% covered by both parts of Medicare.[4]

At present Medicare suffers from a weak financial structure which has been slowly toppling in the past few years. As Senator Robert Dole of Kansas has recently said, "The Medicare trust fund is sure to go broke within a short period of time if we don't take appropriate action."[5] By 1975, ten years after Medicare was instituted, the average cost for treating the elderly rose nearly 300%.[2] Today that figure is much higher. Furthermore, the proportion of the American elderly population is growing as a result of two factors: declining fertility and increasing life spans.[5] With an increasing number of seniors living longer, there exists an increasing demand for federal assistance, leading to a rapid depletion in Medicare funds. This depletion of funds coincides with Administration proposals to lessen the role of the federal government with regard to social welfare programs. For example, Medicare would absorb 64.2% of the fiscal 1983 budget cuts coming from the $3.9 billion used to benefit the nation's elderly.[5]

All this bad news involving the collapsing financial structure of Medicare has led many to speculate that Medicare has become a broken promise to the elderly. The House of Representatives in November 1980 released a report by the Select Committee on Aging concerning the "shortcomings of the Medicare program."[6] The analysis concluded that Medicare "is a highly successful Government program which is currently undergoing severe stress."[6] This stress can most readily be seen in three areas, illustrating very clearly that Medicare has not lived up to its original expectations. The first area involves increasing copayments, or the growing deductibles the elderly must pay in order to receive aid. As shown in Table 1, the costs have escalated astronomically. It is a common myth that Medicare pays for a flat 80% of the elderly's physician's bill after they have satisfied the deductible fee, currently $260. The truth of the matter, however, is best stated by a senior citizen from Oakland, California, in a letter to the *New York Times* appearing October 19, 1982:

> As we over-65'ers have found to our sorrow, Medicare rarely accepts what doctors charge as the basis for calculating the 80 percent . . . Having had considerable experience with these rules, my wife and I have found that we average between 40 and 50 percent Medicare reimbursement of actual physician's fees.

A second area of concern is the trend of fewer doctors accepting assignment of full payment from Medicare for their services. By accepting assignment, a doctor commits himself to accept whatever payment Medicare deems "reasonable."[7] Understandably, physicians do not like to be paid through such uncertain, arbitrary means, and hence the burden rests on the patient who must pay the doctor in full and then hope for adequate reimbursement directly from Medicare.

A third factor causing problems for the elderly concerns just what services are covered by Medicare. The program is designed to cover serious health problems, but it fails to cover a great deal of comparatively minor needs that stack up for the typical senior, including drugs prescribed for outpatients, dental care, eyeglasses and eye examinations, hearing aids and examinations, preventive services such as routine physical examinations and long-term institutional needs.[7] It can thus be seen that a program intended to aid the elderly with the high cost of health care denies reimbursement for those services this group demands most.

Although the future of Medicare is uncertain at best, a variety of possible solutions to the many problems mentioned above have been proposed during the past few years. One of the more popular alternatives would not only bolster Medicare, but would also solve the Medigap abuses in one giant swoop: the addition of a Part C to the original draft.[8] Claude Pepper, Chairman of the Select Committee on Aging, describes Part C:

> It would be voluntary like Part B and funded by a premium equal to Part B. Additional revenues would be carried by a small excise tax on cigarettes and alcohol. Congress could, in effect, authorize a comprehensive Medicare supplemental health insurance policy which would cover eyeglasses, dental care, hearing aids and out-of-hospital prescription drugs. The measure would essentially be self-financing.[8]

Quite simply, Part C would eliminate the need for Medigap policies, and the abuses which exist today would end. The elderly would no longer have to fill the gaps on their own; instead, centralization under

TABLE 1.—*Medicare Premium Costs, Deductibles and Coinsurance Rates (1966, 1981 and 1982)*

Cost Sharing Requirement	*1966*	*1981*	*1982*
Hospital insurance deductible (Part A)	$40.00	$204.00	$260.00
Monthly premium (Part A)*	NA	$ 89.00	$113.00
Hospital co-insurance 61st-90th day	$10.00/day	$ 51.00/day	$ 65.00/day
Co-insurance (60 "lifetime" reserve days) ...	$20.00/day	$102.00/day	$130.00/day
Co-insurance (21st-100th day, SNF care) ...	$ 5.00/day	$ 25.50/day	$ 32.50/day
Medical insurance premium (Part B)	$ 3.00/mo†	$ 11.00/mo†	$ 12.20/mo†
Medical insurance deductible (Part B)	NA	$ 60.00	$ 75.00‡

SNF=skilled nursing facility

*For those 65 or older who are eligible for Social Security benefits.
†Effective July 1 of calendar year.
‡First increase since 1973.
Adapted from Merritt and Potemken.[9]

the federal government would provide every American with uniform benefits.

The Reagan administration is thinking along different lines. Government analysts claim that runaway costs will not be checked until patients who can afford to are instructed to pay a bigger share. This concept, called a means test, would link benefits to income and wealth, with most Americans contributing some part of the first few thousand dollars of their medical bills. In September 1982 the Senate, however, voted 70 to 29 to reject any means test in Medicare.

Another option would "set fixed payment rates for 467 diagnostic categories, ranging from hemorrhoids to heart attacks" (*The Wall Street Journal,* November 17, 1982, p 1). Yet studies of the hospitals in New Jersey which have had such a program since 1981 show that only one in 26 said fixed rates have truly lowered costs (*The Wall Street Journal,* November 17, 1982, p 1). Essentially, these "diagnosis related groups," or DRGs, create an incentive for hospitals to hold down costs, but the quality of care has been questioned (J. Iglehart, lecture, Brown University November 18, 1982). Based on the many problems faced in New Jersey with DRGs, this alternative seems an unlikely one.

Despite these potential cures for Medicare's ailments, however, the fact still remains that because little is being done at present, the need for Medigap coverage increases daily. Until some other plan can be enacted, the elderly can buy into three kinds of Medigap policies: the exclusive Medicare supplement, the indemnity and the limited or dread disease policy.[9]

Medicare supplement policies are forms of "wrap-around coverage," designed to pay for some of Medicare's deductible and coinsurance requirements and assorted payments not otherwise covered. None of these policies cover physician charges above the rates allowed by Medicare, or services such as routine check-ups and custodial care.

Indemnity policies pay a fixed amount for each day in hospital. Yet these benefits are not structured to reflect the actual charges for an inpatient stay in a hospital. With the average cost of a day of hospital care at $266 in 1981,[9] the usual indemnity benefit of $20 to $50 a day fails to provide any true protection for a patient. Moreover, considering that in 1979 the average hospital stay for those over 65 was 11.5 days, the amount of aid given by an indemnity policy is quite limited.[3]

Perhaps the most shockingly unfair form of Medigap coverage is the limited or dread disease policy. Cancer insurance is the most prevalent kind of limited policy. The main reason these policies are unjust rests in the fact that most benefits are geared toward hospital admission (thus technically making them a subset of the indemnity policy). In selling their limited policies, agents promise their company will pay $60 per day for the first 12 days the patient is confined in a hospital with cancer, and $40 per day thereafter. This seems attractive to the consumer because there is no limit to the number of confinements, and for each new admission to the hospital the policy starts again by paying $60 per day. What is not mentioned is that the average stay in a hospital is only about seven days and the average patient with cancer is only admitted to hospital 1.8 times in a two-year period.[3] Unfortunately, the rate of return to limited policyholders is so low that only one in six people in whom cancer actually develops ever break even on the money paid in premiums. Two states, Connecticut and New Jersey, have already prohibited the sale of these policies because of their questionable worth.

The elderly's plight is worsened when Medigap policies have a preexisting clause, or a clause that limits or excludes payment for conditions existing at the time of purchase.[9] Because many elderly persons have long-term illnesses (and recall that Medicare coverage is not equipped for long-term payment), this clause can void much of their insurance protection. Moreover, it is common practice for the elderly to buy new coverage and discontinue what they have, simply because they are rarely satisfied with what is paid for when a policy is put to the test. In purchasing new policies, many seniors are left totally uninsured because one preexisting clause or another is always in effect. In essence, they may give up on a poor policy and spend their money on one that is worthless.

In an effort to better inform Medicare recipients about the pitfalls of Medigap policies, several voluntary and government-sponsored measures have arisen. The National Association of Insurance Commissioners in 1979, for example, enforced the drafting of model state regulations governing Medicare supplements. The Health Care Financing Administration (HCFA) conducts a nationwide training program for volunteers to assist Medicare beneficiaries wishing help in considering the purchase of Medigap coverage. By late 1981 HCFA had prepared more than 13,000 persons in each state to serve the elderly in this manner.[9] HCFA's Office of Public Affairs is also preparing a public service campaign to acquaint beneficiaries of Medicare with state regulatory programs regarding Medigap policies. This campaign has thus far been very successful in reaching out to the nation's seniors, providing them with important information about supplemental insurance. In addition, HCFA created a Medigap Operations Staff (MOS) which maintains contact with private insurance companies and keeps them aware of progressing developments of laws and regulations and how they will affect the companies' modes of operation.

Of more significance, however, is the adoption in 1980 by the United States Congress of the Baucus Amendment creating a Voluntary Certification Program (VCP) for Medigap policies. The law requires the Health Care Financing Administration to set up the federal VCP and provide technical and administrative support to the Supplemental Health Insurance Panel (SHIP). Also, the program studies what regula-

tory measures states have taken toward Medigap policies and provides information to Medicare beneficiaries concerning the purchase of private health insurance.[9]

Criteria for certification include a statement guaranteeing that the specified policy will cover a major portion of Medicare Part A and Part B coinsurance charges. Second, there is a guarantee that the policy "will pay what it says it will pay."[9] Third, certification is a statement that the policy does not contain preexisting clauses of more than six months. Fourth, it ensures that the policy is supplied with a detailed disclosure statement of all coverage, costs and limits, thus making it a bit simpler for the buyer to evaluate policy worth and comparison shop. Lastly, with certification the purchaser can return the policy with full premium refund within ten days of sale. Therefore it appears that certification confronts many of the biggest problems facing the nation's seniors when they search for Medigap coverage.

While VCP has several fine attributes, it also has its shortcomings. It fails to make supplemental policies more affordable and it does not remedy marketing abuses.

In addition to the federal programs, the states have passed at least some token legislation involving Medigap abuses which at first glance looks impressive. Upon closer study, however, it becomes clearer that the states simply cannot devote the time, energy and funds needed to truly enforce their goals of licensing all agents and prohibiting sales methods that "misrepresent the benefits, advantages, conditions, or terms of an insurance policy."[9] Beyond the problem of a proper means of enforcement, the abuses continue because older victims of dishonest agents are usually poor witnesses in criminal enforcement proceedings.

The future of the Medigap program rests mostly on whatever impact the Voluntary Certification Program makes on the health care community. Ideally, the future may bring much better informed Medicare consumers, having an increased awareness of supplemental insurance plans. It is hoped that certification will make it easier for buyers to identify good policies and make wiser choices regarding their purchases. Most analysts hope the Voluntary Certification Program has a short, but effective, future. When all states have complied by enacting a uniform set of programs, then involvement of the federal program will no longer be needed. As it stands today, many states interpret the Voluntary Certification Program as federal interference and an assault on their autonomy. Yet it is generally accepted that the program will be necessary until all 50 states enforce equivalent laws that protect the nation's senior citizens. The coming months will present an extreme test for the Reagan administration as well. No one can evaluate at this stage if the Voluntary Certification Program will be successful. There are many groups in favor of ending government's role in medical issues, while others favor expansion. Whichever view prevails, it appears from the numerous problems of Medigap policies dealt with in this paper that the situation will not simply remedy itself.

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SUPPLEMENTAL READING

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

CHEST MEDICINE—Edited by Ronald B. George, MD, Louisiana State University Medical Center, Shreveport; Robert W. Light, MD, Veterans Administration Medical Center, Long Beach, California, and University of California, Irvine, and Richard A. Matthay, MD, Yale University School of Medicine, New Haven, Conn. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 657 pages, $49.50,

At a time when several new textbooks have appeared on chest diseases, this is yet another multiple author textbook on chest medicine. According to the authors, the book is designed for use by nursing and respiratory therapy students, as well as housestaff physicians and fellowship trainees in pulmonology and related fields.

The book is organized into three sections: pulmonary structure and function, collecting the data base and clinical patterns of lung disease. The first section deals primarily with physiological principles, is well-referenced and is succinct. Due to limitations imposed by the size of the book, some aspects are covered too briefly, but the references allow the reader to go to other appropriate sources for further details.

The second section on collecting the data base covers the basics of history and physical examination, chest radiology, clinical pulmonary function testing, exercise and disability evaluation, and other diagnostic techniques. Some aspects are dealt with in greater detail than others—computerized axial tomography gets a paragraph, while a radiograph of a barium swallow demonstrating an enlarged left atrium occupies half a page. As with the first section, the references are up to date and pertinent.

The third section of the book on clinical patterns of lung disease covers the expected areas of clinical lung diseases. This section, by virtue of its size, covers some areas in a sketchy fashion, but the ample references make up for these deficiencies.

In conclusion, the book is a good start for the student to be introduced to pulmonary diseases, and the references guide him to selected further reading. Persons more advanced in their training, such as pulmonary fellows, may have to go to the references to get a more detailed account of a specific topic.

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* * *

BASIC & CLINICAL PHARMACOLOGY—Edited by Bertram C. Katzung, MD, PhD, Professor of Pharmacology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 815 pages, $23.50.

Basic and Clinical Pharmacology, edited by Bertram G. Katzung, MD, PhD, is an entirely new textbook that is available in paperback form. This is one of the Lange Series books and supersedes the *Review of Medical Pharmacology,* by Frederick Meyers, Ernest Jawetz and Alan Goldfein. The book is by no means small (815 pages), but the chapters are concise and readable. This book is not meant to be an encyclopedia of pharmacology. For that, readers are referred to standard pharmacology texts.

Basically, I found the book to be very readable and appropriate to serve as a primary text for a number of pharmacology courses. It includes what many teachers would include in a lecture on certain types of drugs. It does not have the in-depth treatment that is necessary to pursuc questions beyond those presented in a lecture or in this book.

Each chapter includes a section on clinical pharmacology of the specific agents that have already been discussed. This appears to be a somewhat artificial separation in that half-life and disposition are included in the "basic pharmacology" and not in the clinical pharmacology section. In general, the clinical pharmacology sections are not terribly useful. They are too brief to really guide therapy. In addition, some of the chapters have overlap in the basic and clinical pharmacology sections within the same chapter. For instance, the chapter discussing vasodilators and angina pectoris discusses the drugs twice and it is difficult to get an overall picture without flipping back and forth between the so-called basic and clinical pharmacology sections. In subsequent editions perhaps this organization should be reexamined.

Nonetheless, the book is an admirable attempt to present a concise and useful compendium of pharmacology. The contributing authors are as outstanding a group as has been assembled for a pharmacology textbook. This book looks like a winner and should be useful for medical students and students in other health professions such as nursing and pharmacy, and as a quick reference for housestaff and practicing physicians.

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* * * *

PLATELETS: PATHOPHYSIOLOGY AND ANTIPLATELET DRUG THERAPY—Harvey J. Weiss, MD, Professor of Medicine, College of Physicians and Surgeons of Columbia University; Director, Division of Hematology-Oncology, St. Luke's-Roosevelt Hospital Center, New York. Alan R. Liss, Inc. 150 Fifth Ave., New York, NY 10011, 1982. 165 pages, $22.00.

This slender volume of 165 pages devotes 55 of them to the reference list and index. That fully 25% of a book is devoted to a reference list, suggests that the author, a distinguished platelet researcher, wanted to document each statement with exquisite care. Although he has succeeded in doing so, it is at the expense of readability. The first 70-odd pages are devoted to a fundamental review of platelet physiology, biochemistry and the pharmacology of antiplatelet drugs. A great deal of material is covered, but in a dry, pedantic fashion. In all those pages, there are only six illustrations: one electron micrograph of a platelet, three rather elementary diagrams and two tables. The reader seeking to develop a clearer understanding of the participation of platelets in hemostasis of blood coagulation, or their interaction with the endothelium and its appurtenances, will have to dig it out of text. There is little sense of the dynamic, sequential series of events that occur, and that could be depicted well diagrammatically. Similarly, those seeking an overview of endoperoxide/prostaglandin biochemistry are forced to read rather than *see* the interrelationships. Even for the pharmacology of platelet inhibitors there is no diagram illustrating the site at which the various agents work. It is a matter of style, and Dr Weiss obviously prefers a descriptive rather than an illustrative approach.

The final section of 32 pages critically reviews a series of published studies dealing with the effectiveness (or lack thereof) of platelet inhibitors in cerebrovascular and cardiovascular disease. It also has brief paragraphs dealing with various other disorders (for example, thrombotic thrombocytopenic purpura and venous thrombosis) for which these agents have been uti-

lized. This section may be useful to those seeking a concise yet critical review of these topics. Those who wish more detailed review can utilize the extensive reference list. Most of the references date from the 1970s and before, with 10% bearing a date of 1980 or later. That's par for the course in most hard-cover books.

For readers seeking a detailed, well-documented review of fundamental platelet physiology and biochemistry/pharmacology, it is here if one can devote the effort to heavy reading. Those seeking a less-detailed and more dynamic overview will find this book heavy going. Finally, those seeking clinical guidance will find the final section a useful but brief introduction to the state of the art. For specific guidance on clinical problems, there is little help here. If you wish to know the value of measuring circulating platelet aggregates, for example, it is mentioned, but there is no critical discussion. Or if you want information on heparin thrombocytopenia, it too is mentioned, but with only a single reference (the book's reference number 460, and that paper does *not* deal with heparin-induced thrombocytopenia, but with in vitro heparin induced platelet aggregation).

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NEUROLOGY FOR NON-NEUROLOGISTS—Edited by Wigbert C, Wiederholt, MD, Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla, Calif. Academic Press, Inc., 111 Fifth Ave., New York, NY 10003, 1982. 400 pages, $37.50.

This concise textbook provides an excellent introduction to the field for medical students as well as a useful guide for general physicians interested in a variety of neurological topics. The multi-authored volume includes chapters dealing with the neurological history and examination of both adult and pediatric patients. There is a section devoted to laboratory studies in neurological disease. This includes chapters on lumbar puncture, spinal fluid examination, electromyography, electroencephalography, evoked potentials, neuroradiology and neuropsychological testing. The remainder of the book deals with specific neurological disorders including headache, stroke, dementia, demyelinating disorders, motor system diseases, the metabolic encephalopathies, the myopathies, neuropathies, seizures, Parkinson's Disease, infections, dizziness and vertigo, congenital anomalies, hereditary disorders, learning disability, tumors, cranial and spinal trauma and radiculopathies. A large number of useful tables have been included. The bibliographies in each chapter are terse. With 11 individual authors, the writing of the book is somewhat uneven; however, the authors have assembled a very useful, practical guide to the field for the nonspecialist.

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* * *

MYOCARDIAL INFARCTION—ITS PRESENTATION, PATHOGENESIS AND TREATMENT—Robin M. Norris, MB, ChB(NZ), MD(Birm), FRCP(Lond), FRACP, Physician in Charge, Coronary Care Unit, Green Lane Hospital, Auckland, New Zealand, and Honorary Associate Professor, Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 316 pages, $49.00.

The monograph contains 27 chapters with the text being divided into three parts. Part I is titled "Natural History of Myocardial Infarction" and contains 13 chapters ranging from coronary risk factors to electrocardiogram cardiac enzymes and radionuclide scanning in myocardial infarction. Part II contains six chapters dealing with the treatment of myocardial infarction and Part III has several chapters on the experimental models of infarction and their applicability to clinical practice.

The majority of the chapters have been written by Dr Norris alone or in coauthorship with others. The chapters are well organized, brief, to-the-point and well referenced; the most recent references are 1980. The chapters on clinical presentations, disorders of cardiac function during and after infarction, arrhythmias in acute myocardial infarction, conduction disturbances due to infarction, complications of myocardial infarction and prognosis after myocardial infarction are very well presented. The chapter on acute coronary care outlines the concepts of immediate care and the management of arrhythmias.

The first two parts of the book are clinically oriented and provide readers with considerable amounts of information on the pathophysiology and natural history of myocardial infarction and should be valuable to internists with responsibility for treating patients with acute myocardial infarction. Also, there is valuable information for practicing cardiologists.

One apparent weakness of the book lies in the lack of adequate emphasis on the pharmacology and pharmacokinetics of various drugs used in acute myocardial infarction, although a reasonable review is presented in Chapter 16 titled "Treatment for Complications of Infarction." Also a chapter each on anticoagulant, antithrombotic and antiplatelet drugs in myocardial infarction and one on the place of cardiac surgery in myocardial infarction is included. A detailed mention of the role of thrombolytic therapy and the use of percutaneous transluminal coronary angioplasty in acute myocardial infarction would have enhanced the text.

ZAKUDDIN VERA, MD
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* * * *

CLINICAL ETHICS: A Practical Approach to Ethical Decisions in Clinical Medicine—Albert R. Jonsen, PhD, Professor of Ethics in Medicine, Department of Medicine, University of California, San Francisco; Mark Siegler, MD, Associate Professor of Medicine, Section of General Internal Medicine, Pritzker School of Medicine, University of Chicago; and William J. Winslade, PhD, JD, Co-Director, Program in Medicine, Law and Human Values, Adjunct Professor of Law, School of Law, and Adjunct Professor of Psychiatry, UCLA School of Medicine, Los Angeles. Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022, 1982. 187 pages, $18.00.

This small volume is one of those rare medical texts that deserves to be read from cover to cover as well as for reference. The initial reading, which can be accomplished in just a few hours, is enjoyable because the book systematically analyzes and clarifies many of the gray areas in the patient-physician encounter that in many ways cause the physician more stress than do decisions about purely clinical problems. It is a useful guide for physicians who have to make judgments. The major headings are (1) indications for medical intervention, (2) preference of patients, (3) quality of life and (4) external factors. The book is particularly helpful on questions involving prolonging of life, specifically on orders not to resuscitate, and on autonomy of the patient, truthful disclosure and use of placebos.

Uniformly excellent and brief clinical case presentations are followed by a discussion "comment" and finally by "counsel" in which the three authors—a professor of ethics, a physician and an attorney—give their carefully weighed opinions. The book identifies three types of encounters: acute life-threatening disorders, chronic lethal disease and chronic debilitating disease; it meticulously dissects the specific problems that each of these situations entail. The authors do not hesitate to acknowledge the occasional dilemma, when no easy answer is available; for instance, in the area of confidentiality. They sometimes suggest that some particularly difficult questions cannot be solved either by physician or patient but may require an outside review committee's help. In a general way the authors stress the need to elicit the patient's preference and inclinations. Although a special chapter is devoted to external factors, most decisions are in the hands of the physician and the patient; patient's relatives have rather little authority.

The book certainly belongs in every internist's office, especially those subspecialists who see many dying patients. It would grace any morning report session, and might be particularly helpful to chairmen of departments of medicine, to remind everybody that decision-making involves many personal considerations in addition to hard medical facts.

RALPH O. WALLERSTEIN, MD
Clinical Professor of Medicine and Laboratory Medicine
University of California, San Francisco

In Memoriam

California Medical Association

EPSTEIN, LEONARD, Hayward. Died August 27, 1983, of injuries received in a light plane crash in Southern Contra Costa County, California, aged 48. Graduate of the University of Pittsburgh School of Medicine, Pittsburgh, 1960. Licensed in California in 1963. Dr Epstein was a member of the Alameda-Contra Costa Medical Association.

HAVEMANN, ELSIE M., Monrovia. Died March 15, 1983, aged 95. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1921. Licensed in California in 1927. MD degree from California College of Medicine, 1962. Dr Havemann was a member of the Los Angeles County Medical Association.

HERSHENSON, HERBERT L., Los Angeles. Died May 7, 1983, aged 80. Graduate of Marquette University School of Medicine, Milwaukee, 1929. Licensed in California in 1940. Dr Hershenson was a retired member of the Los Angeles County Medical Association.

KATZ, EDWARD E., Los Angeles. Died March 28, 1983, aged 53. Graduate of Université de Lausanne Faculté de Médecine, 1956. Licensed in California in 1963. Dr Katz was a member of the Los Angeles County Medical Association.

LYON, CLAYTON G., San Franeisco. Died July 30, 1983, in Richmond, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr Lyon was a retired member of the San Francisco Medical Society.

MCLENNAN, ROBERT M., Pebble Beach. Died April 4, 1983, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1943. Licensed in California in 1943. Dr McLennan was a member of the Los Angeles County Medical Association.

MORGAN, THOMAS L., JR, San Pedro. Died May 20, 1983, aged 59. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. MD degree from California College of Medicine, 1962. Dr Morgan was a member of the Los Angeles County Medical Association.

OETTINGER, LEON, JR, San Marino. Died April 22, 1983, aged 65. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1942. Licensed in California in 1948. Dr Oettinger was a member of the Los Angeles County Medical Association.

ORENSTEIN, MARTIN M., Pacific Palisades. Died May 28, 1983, aged 41. Graduate of the University of Michigan Medical School, Ann Arbor, 1966. Licensed in California in 1967. Dr Orenstein was a member of the Los Angeles County Medical Association.

SILVERTHORNE, JOHN D. II, Long Beach. Died April 24, 1983, aged 60. Graduate of Southwestern Medical School of the University of Texas, Dallas, 1952. Licensed in California in 1953. Dr Silverthorne was a member of the Los Angeles County Medical Association.

Washington State Medical Association

DODGSON, THOMAS B., Stanwood. Died February 15, 1983, in Stanwood, aged 74. Graduate of the University of Oregon Medical School, Portland, 1934. Licensed in Washington in 1941. Dr Dodgson was a retired member of the Snohomish County Medical Society.

KEIM, SILAS A., Wenatchee. Died March 27, 1983, aged 92. Graduate of Northwestern University Medical School, Chicago, 1925. Licensed in Washington in 1925. Dr Keim was a retired member of the Chelan-Douglas County Medical Society.

LYNBERG, RAYMOND A., Spokane. Died October 14, 1982, in Spokane, aged 56. Graduate of Ohio State University College of Medicine, Cincinnati, 1953. Licensed in Washington in 1955. Dr Lynberg was a member of the Spokane County Medical Society.

MURPHY, JOHN B., Cheney. Died June 9, 1983, in Cheney, aged 64. Graduate of the University of Ottowa School of Medicine, Ottowa, Ontario, 1957. Licensed in Washington in 1958. Dr Murphy was a member of the Spokane County Medical Society.

OSBORNE, ROBERT WESLEY, Tacoma. Died in September 1982 in Tacoma, aged 62. Graduate of Indiana University School of Medicine, Indianapolis, 1944. Licensed in Washington in 1952. Dr Osborne was a member of the Pierce County Medical Society.

PIPER, WAYNE L., Ephrata. Died February 2 1983, in Ephrata, aged 57. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1953. Licensed in Washington in 1954. Dr Piper was a member of the Grant County Medical Society.

REID, ROBERT P., Spokane. Died June 26, 1983, in Spokane, aged 59. Graduate of the University of Toronto Faculty of Medicine, 1953. Licensed in Washington in 1954. Dr Reid was a member of the Spokane County Medical Society.

TAYLOR, THOMAS J., Olympia. Died May 4, 1983, in Olympia, aged 69. Graduate of the University of Oregon Medical School, Portland, 1940. Licensed in Washington in 1941. Dr Taylor was a member of the Thurston-Mason County Medical Society.

WARD, KENNETH CHARLES, Sequim. Died in June 1983 in Sequim, aged 77. Graduate of the University of Colorado School of Medicine, Denver, 1935. Licensed in Washington in 1936. Dr Ward was a retired member of the Grant County Medical Society.

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

PLATELETS: PATHOPHYSIOLOGY AND ANTIPLATELET DRUG THERAPY—Harvey J. Weiss, MD, Professor of Medicine, College of Physicians & Surgeons of Columbia University; Director, Division of Hematology-Oncology, St. Luke's-Roosevelt Hospital Center, New York. Alan R. Liss, Inc., 150 Fifth Ave., New York, NY 10011, 1982. 165 pages, $22.00.

THE POLITICS OF REPRODUCTIVE RITUAL—Karen Ericksen Paige & Jeffery M. Paige. University of California Press, 2223 Fulton St., Berkeley, CA 94720, 1983. 380 pages, $8.95 (softbound).

PRACTICAL MANAGEMENT OF EMOTIONAL PROBLEMS IN MEDICINE—Revised Edition—Hugh James Lurie, MD, Clinical Professor of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle. Raven Press, 1140 Avenue of the Americas, New York, NY 10036, 1982. 243 pages, $24.00.

PRACTICAL PULMONARY DISEASE—Edited by Irwin Ziment, MD, Professor, Department of Medicine, University of California, Los Angeles, School of Medicine, and Chief, Department of Medicine, Olive View Medical Center, Van Nuys, California. John Wiley & Sons, Inc., One Wiley Drive, Somerset, NJ 08873, 1983. 218 pages, $14.95.

A PRIMER OF ORTHOPAEDIC BIOMECHANICS—George Van B. Cochran, MD, MScD, Director, Orthopaedic Engineering and Research Center, Helen Hayes Hospital, West Haverstraw, NY; Professor of Clinical Orthopaedic Surgery, College of Physicians and Surgeons, Columbia University, New York. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 413 pages, $48.00.

PRINCIPLES OF PEDIATRIC PHARMACOLOGY—Volume Six of MONOGRAPHS IN CLINICAL PHARMACOLOGY—Lars O. Boréus, MD, Professor and Chairman, Department of Clinical Pharmacology, Karolinska Hospital, Stockholm. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 212 pages, $32.00.

PRINCIPLES AND PRACTICE OF BLOOD-GAS ANALYSIS—A. P. Adams, PhD (LOND), MB, BS, MRCS, LRCP, FFA, RCS, DA, Professor of Anaesthetics in the University of London, Guy's Hospital Medical School, London, and C. E. W. Hahn, MA, D Phil (OXON), MSc, BSc, University Lecturer in Anaesthetics, Nuffield Department of Anaesthetics, University of Oxford. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036. 95 pages, $19.50 (softbound).

PULMONARY EMERGENCIES—Edited by Steven A. Sahn, MD, Associate Professor of Medicine, University of Colorado Health Sciences Center; Attending Physician, Medical Intensive Care Unit, University Hospital; Director, Pleural Space Laboratory, Webb-Waring Lung Institute, Denver. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 415 pages, $42.00.

RADIOLOGY OF SKELETAL TRAUMA—Volumes 1 & 2—Lee F. Rogers, MD, Professor and Chairman, Department of Radiology, Northwestern University Medical School, Chicago. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 920 pages, $175.00.

REAL-TIME ULTRASONOGRAPHY—Volume 10 of CLINICS IN DIAGNOSTIC ULTRASOUND—Edited by Fred Winsberg, MD, Professor, Department of Diagnostic Radiology, McGill University Faculty of Medicine, Diagnostic Radiologist-in-Chief, Montreal General Hospital; and Peter L. Cooperberg, MD, Associate Professor, Department of Radiology, University of British Columbia Faculty of Medicine, Chief, Section of Ultrasound, Department of Diagnostic Radiology, Vancouver General Hospital. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 321 pages, $27.00.

RECENT DEVELOPMENTS IN CARDIOVASCULAR DRUGS—Edited by John Coltart, MD, MRCP, FACC, Consultant Physician in Cardiology, St. Thomas' Hospital, London, and David E. Jewitt, BSc, MB, BS, FRCP, Director of Cardiac Department and Consultant Cardiologist, King's College Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 348 pages, $59.00.

SEGMENTAL ANATOMY—Application to Clinical Medicine—Marvin Wagner, MD, MS (Anatomy), Clinical Professor of Surgery and Clinical Professor of Anatomy, Medical College of Wisconsin, Milwaukee, and Thomas L. Lawson, MD, Professor of Radiology and Chief, Section of Computed Body Tomography and Ultrasonography, Medical College of Wisconsin, Milwaukee. 650 pages, $95.00, 1982, Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022.

THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE—Paul Starr, PhD, Associate Professor of Sociology, Harvard University, Cambridge. 514 pages, $24.95, 1982, Basic Books, Inc., Publishers, 10 East 53rd St., New York, NY 10022.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

SOURCEBOOK ON FOOD AND NUTRITION—Third Edition—Contributing Editors: Ioannis S. Scarpa, PhD, Chairman, Department of Biochemistry, School of Dentistry, Loyola University, Chicago; Helen Chilton Kiefer, MD, PhD, currently in postgraduate training in medicine; and Rita Tatum, freelance journalist. Marquis Who's Who, Incorporated, 200 East Ohio Street, Chicago, IL 60611, 1982. 549 pages, no price given.

STAND TALL!—The Informed Woman's Guide to Preventing Osteoporosis—Morris Notelovitz, MD, PhD, and Marsha Ware, with illustrations by Jeff Erickson. 208 pages, $12.95 (hardcover), $6.95 (paperback), 1982, Triad Publishing Company, Inc., PO Box 13096, Gainesville, FL 32604.

THE SUICIDAL PATIENT: RECOGNITION, INTERVENTION, MANAGEMENT—Victor M. Victoroff, MD. Medical Economics Books, 680 Kinderkamack Road, Oradell, NJ 07649, 1983. 254 pages, $24.50.

THORACIC ANESTHESIA—Edited by Joel A. Kaplan, MD, Professor, Department of Anesthesiology; Director, Division of Cardiothoracic Anesthesia, Emory University School of Medicine, Atlanta. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 762 pages, $79.00.

TUBULO-INTERSTITIAL NEPHROPATHIES—Volume 10 in CONTEMPORARY ISSUES IN NEPHROLOGY series—Ramzi S. Cotran, MD, Professor of Pathology, Harvard Medical School, and Chairman, Department of Pathology, Brigham and Women's Hospital, Boston. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 357 pages, $49.50.

URORADIOLOGY: AN INTEGRATED APPROACH—Volumes 1 & 2—Edited by Gerald W. Friedland, MD, FRCP (Edin), FRCR; Roy Filly, MD; Michael L. Goris, MD, PhD; David Gross, MD; Richard L. Kempson, MD; Melvyn Korobkin, MD; Barton D. Thurber, PhD; Joseph Walter, MD. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 1,760 pages, $190.00.

GUIDE TO DIAGNOSTIC IMAGING—VOLUME 2—GALLBLADDER & BILIARY SYSTEM—Alexander Kovac, MD, Chief, Radiology Service, and Adjunct Assistant Professor of Radiology; Robert A. Sanowski, MD, Chief, Gastroenterology Section, and Associate Clinical Professor of Medicine, and Richard A. Kozarek, MD, Assistant Chief, Gastroenterology Section, and Associate Clinical Professor of Medicine, Veterans Administration Medical Center, Phoenix, and University of Arizona College of Medicine, Tucson. Medical Examination Publishing Co., Inc., 969 Stewart Avenue, Garden City, NY 11530, 1983. 237 pages, $33.00.

GUIDE TO DIAGNOSTIC IMAGING—VOLUME 3—PANCREAS—Alexander Kovac, MD, Chief, Radiology Service, and Adjunct Assistant Professor of Radiology, and Richard A. Kozarek, MD, Assistant Chief, Gastroenterology Section, Veterans Administration Medical Center, Phoenix, and University of Arizona College of Medicine, Tucson. Medical Examination Publishing Co., Inc., 969 Stewart Avenue, Garden City, NY 11530, 1983. 205 pages, $33.00.

HEMOSTASIS & THROMBOSIS: A CONCEPTUAL APPROACH—2nd Edition—Jack Hirsh, MD, Professor and Chairman of the Department of Medicine, and Elizabeth A. Brain, MD, Learning Resources Editor, Faculty of Health Sciences, McMaster University, Hamilton, Ontario. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 164 pages, $12.00 (softbound).

A SYNOPSIS OF HAEMATOLOGY—John D. M. Richards, MA, MD, FRCP, FRC Path; David C. Linch, BA, MB, BChir, MRCP, and Anthony H. Goldstone, MA, FRCP (Edin), MRCPath, Department of Haematology, University College Hospital, London. John Wright, PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 320 pages, $19.50 (softbound).

A TEXTBOOK OF EPILSPSY—2nd Edition—John Laidlaw, FRCP, (Edin), Consultant Physician to Epilepsy Centre, Quarrier's Homes, Bridge of Weir, and Alan Richens, PhD, FRCP, Professor of Pharmacology and Materia Medica, Welsh National School of Medicine, Cardiff, Wales. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 544 pages, $59.00.

THE ZERO PEOPLE—Edited by Jeff Lane Hensley. Servant Books, Box 8617, 840 Airport Blvd., Ann Arbor, MI 48107, 1983. 310 pages, $7.95 (softbound).

ACCESS TO THE WORLD—A TRAVEL GUIDE FOR THE HANDICAPPED—Louise Weiss. Facts on File, Inc., 450 Park Avenue South, New York, NY 10016, 1983. 216 pages, $14.95.

ADOLESCENT MEDICINE—Edited by Adele E. Hofmann, MD, Director, Adolescent Medical Unit, Department of Pediatrics, New York University Medical Center and Bellevue Hospital Center, and Associate Professor of Pediatrics, New York University School of Medicine, New York. Addison-Wesley Publishing Company, Medical/Nursing Division, Sand Hill Road, Menlo Park, CA 94025, 1983. 442 pages, $35.00.

(Continued on Page 980)

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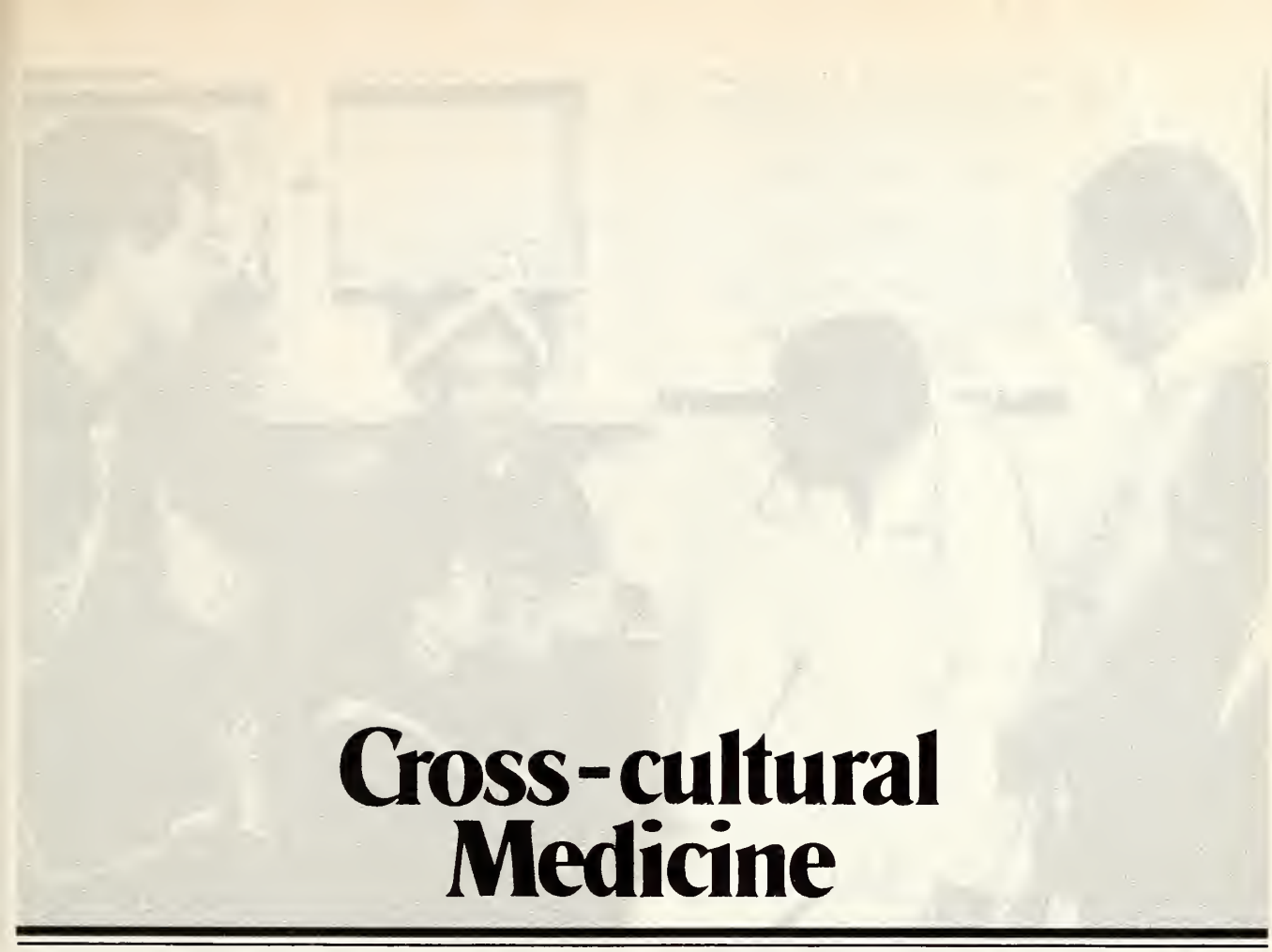

Cross-cultural Medicine

An Emerging Facet of the Medical Art

THIS SPECIAL ISSUE is devoted to what we are calling cross-cultural medicine. It is a recognition of the fact that physicians, particularly those practicing in the western states, but many in other parts of the country as well, are finding themselves caring for patients who are from cultures other than their own and who have not yet been assimilated in what we think of as the American melting pot. Medical anthropology has only recently begun to develop as an important discipline with important implications for physicians who are practicing mainstream medicine in America. M. Margaret Clark, PhD, is widely known for her research in this academic discipline, and as Special Editor for this issue has prevailed upon some of her colleagues to prepare articles in their special fields of interest for publication here. It is her hope, equally shared by the editors, that these articles will whet the interest of practicing physicians in learning more about the beliefs and practices of persons from other cultures who may be their patients. Such knowledge can often significantly affect the outcome of the treatment such patients receive when they are under the care of a Western trained physician.

It is worth reminding ourselves that we physicians also have a distinct culture of our own, one which separates us from many patients of whatever culture, and to some extent even from the society we serve. This produces communications difficulties in the day-to-day care of some and perhaps even most of our patients, even though we think of them as having the same cultural background as our own. The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background.

Too little attention has been paid and too little study has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care. This issue of *The Western Journal of Medicine* will have served its purpose if it calls the attention of physicians, and perhaps others, to what has as yet been a largely unexplored component of the medical art. Cross-cultural medicine is surely becoming a challenge to our Western tradition of patient care, and we are indebted to Dr Clark for giving us a glimpse into this important field of medical knowledge which is only just beginning to take shape.

MSMW

Cultural Context of Medical Practice

SPECIAL GUEST EDITOR
M. MARGARET CLARK, PhD

One of the most striking characteristics of the contemporary American West is the number and variety of ethnic minority group members who make it their home. There has been a steady growth of migrant and immigrant populations in the western states for more than a century. While the overall US population is rapidly expanding, growing by 6% between 1970 and 1980, the West has increased at an even more rapid rate. Rates of growth for individual states range from a low of 13.3% in Montana to a high of 63.5% in Nevada.[1] During the 1970s, furthermore, the number of minority group members increased at a much more rapid rate than did the US population generally. Blacks grew by 17.3%, Native Americans and Hispanics* by even more, and the number of Asian and Pacific Island peoples more than doubled in the ten-year period.[2] With the exception of blacks, all major ethnic groups are heavily overrepresented in the West (See Table 1). For example, in 1980 42.8% of all Hispanics, 50.7% of Native Americans, 52.7% of Chinese-Americans, 69.3% of Pilipino-Americans† and 80.6% of Japanese-Americans lived in the western states.

Many western US cities contain many tens of thousands of immigrants from every major part of the world. For example, it is estimated that since 1970, 2 million foreign immigrants have settled in the Los Angeles area alone, more than 90,000 of them during the single year of 1982. According to one report, "of L.A.'s 550,000 schoolchildren, 117,000 speak one of 104 languages better than they do English" (*Time*, June 13, 1983, p 20).

With such numbers and such proportions, it is impossible for physicians and other health professionals to ignore the special problems and needs of patients from these communities. These problems are of several kinds: First, many immigrant and refugee populations have higher rates of infectious disease and parasitic infestation than the general population. Furthermore, stress-related disorders are more common in migrant groups who often suffer social, economic and cultural dislocations, as well as discrimination and poverty. Traditionally high birth rates among immigrant families also bring many women and infants into contact with medical institutions. In sum, increasing numbers of minority group patients are likely to find their way into the practices of most physicians in this country, whether in offices, hospitals or clinics. Cultural diversity shows no signs of abating, and medical practitioners are increasingly aware of the problems inherent in transcultural medical practice.

The Nature of Cultural Barriers in Health Care

The papers in this special collection are devoted to an examination of the kinds of problems that arise as a result of disparities between the cultural backgrounds of patients and practitioners. Most of the papers assume that physicians will be middle-class Americans and that their task will be to understand and deal with patients who are not of that background. Of course this is not always the case; by no means are all health practitioners middle-class English speakers. Yet the principles of medical anthropology are just as relevant for minority group practitioners or foreign medical graduates as for anyone else. All major cultural groups contain class or ethnic subgroups whose ideas about illness and proper professional behavior may differ widely. In a pluralistic society such as ours, everyone must find ways to communicate with others whose worlds of symbols and meaning are so different from their own.

In any discussion of ethnic variability and health care, it is important to remember that there are great individual differences within all ethnic communities in health knowledge, attitudes and behavior. Some research has indicated that there may be more discrepancies among persons of different educational and class levels *within* an ethnic category than exist *across* ethnic boundaries, if the individual persons have similar educational and social class backgrounds and are equally familiar with mainstream American life. In general, people of lower socioeconomic status tend to behave "more ethnically" in health matters than do those of

*Census data indicate that the population of Spanish-speaking origin increased by 61.0% and Native Americans by 71.4% between 1970 and 1980; however, these figures are likely inflated because of changes in census procedures.

†*Pilipino* has recently come to be preferred over Filipino by immigrants to the United States for purposes of ethnic identity, in line with the usage adopted by the national language of the Philippines (which does not have the letter "f").

Refer to Clark MM: Cultural context of medical practice. *In* Cross-cultural medicine. West J Med 1983 Dec; 139:806-810.
Dr Clark is Professor of Anthropology, Medical Anthropology Program, University of California, San Francisco, School of Medicine.
Reprint requests to M. Margaret Clark, PhD, Medical Anthropology Program, University of California, 1320 Third Avenue, San Francisco, CA 94143.

TABLE 1.—*Resident Population in Western States by Race and Spanish-Speaking Origin*

Race or Origin	Total US N in Thousands	Western States* N in Thousands	Western States* Percent of Group
Total	226,546.0	43,173.0	19.0
White	188,372.0	34,890.0	18.5
Black	26,295.0	2,262.0	8.5
American Indian†	1,420.4	720.8	50.7
Chinese	806.0	424.8	52.7
Pilipino	774.7	537.0	69.3
Japanese	701.0	565.0	80.6
Asian Indian	361.5	72.0	19.9
Korean	354.6	153.9	43.4
Vietnamese	261.7	119.9	45.8
All other races	6,999.2	3,427.4	49.0
Spanish-speaking origin‡	14,609.0	6,254.0	42.8

[Derived from data presented in US Bureau of the Census. Current Population Reports.[2(p32)]]

* Includes Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Washington, Oregon, California, Alaska and Hawaii.

† Includes Eskimo and Aleut.

‡ Persons of Spanish-speaking origin may be of any race.

higher socioeconomic levels. Also, "the more homogeneous and close-knit social relationships are for individuals within any ethnic group, the less biomedically oriented their health attitudes are likely to be."[3(p12)] This is as true of native English-speaking patients as it is of any other group.

Let me turn now to a brief general discussion of some of the cultural barriers to clinical care that are discussed in the following papers. They deal in the main with five categories: (1) language use and nonverbal communication patterns, (2) medical roles and responsibilities, (3) explanatory models of disease, (4) contextual factors, and (5) emotional impact and stigma. The various papers *in toto* deal with all these topics, although no single article treats all of them. At the end of this article, a set of readings is provided that treats them in fuller detail.

Language Barriers and Communication Patterns

Without language, the work of a physician and that of a veterinarian would be nearly identical. In cases where there is little or no common understanding between patient and practitioner, the necessary use of interpreters is sometimes satisfactory, but in other instances is fraught with difficulties. Lay interpreters may know little medical terminology, and may require careful explanations about the kind of information that is required from the patient. In some instances, interpreters may come from a different educational or social stratum from that of the patient, and social distance and rules of decorum may render communication difficult. In my personal experience, a well-educated or highly acculturated member of an ethnic category is often reluctant to report patients' statements accurately if those statements seem to reflect what the interpreter regards as "ignorance" or "superstition." Much useful medical information can thus be lost. In some cases bilingual adolescent or adult children can be used as interpreters, unless the material to be translated contains information that is a taboo subject for discussion between parent and child (much gynecological information is of this nature). For these various reasons, the language barrier may prove a difficult one. Even so, in cases where an accurate history is essential, it will pay the clinician to take some care in obtaining proper translation.

Nonverbal communication patterns also vary from culture to culture. Hand-shaking and smiling are essential ingredients of productive medical interactions with Latino and working-class black patients, but have been found to signify frivolity and immaturity to Soviet emigrés (see the papers by Snow, by Maduro and by Wheat, Brownstein and Kvitash in this issue). Some attention to traditional patterns of demeanor and decorum will prove a useful addendum to the knowledge of the clinician in interethnic encounters.

Medical Roles and Responsibilities

Much has been written about the expectations that patients from a variety of ethnic backgrounds have of health personnel. In general, members of most ethnic minority groups in this country are unwilling to relinquish to medical personnel complete control over the care of a patient, even in acute care settings. In reports of the behavior of Arab families, for example, patients' beds are described as

> invariably surrounded by relatives and friends. The health care providers are amazed at the number of persons who are constantly in the way of the hospital routine and who seem to interfere with the kind of care the health care personnel prefer to give.[4(p592)]

As several articles in this issue explain (Lipson and Meleis, Kim, Hartog and Hartog, for example) family members and close associates are expected to be near the patient as much as possible, to provide emotional support, to take care of special needs that hospital personnel do not provide (special foods, herbal medicines, massage and the like), and to monitor the medical treatment. These articles demonstrate the kinds of conflicts that often arise when familial roles are neither understood nor accepted by medical personnel.

In some cases, alternative healers are sought to provide supplementary kinds of treatment simultaneously with that of biomedical specialists. Reasons for this behavior are related to ideas about different levels of causality, as discussed below. Family members often arrange through a "lay referral system" for alternative forms of care, as part of their culturally defined obligation to see that their ailing relative has access to a full range of possible cures. In many ethnic communities responsibility for the patient's healing is not "turned over" to the physician but remains with patient and family. As Lock points out in her article on Japanese attitudes: "the physician is a skilled and sympathetic technician," whose role is to assist in the cure, not to take it over. In sum, culturally patterned medical roles influence doctor-patient and other medical relation-

ships by establishing guidelines for what is considered appropriate clinical responsibility and communication.

Explanatory Models of Disease

Explanatory models in all cultures go far beyond ideas about specific pathogens, dislocations, toxins, traumata, degenerations or biochemical imbalances. They are broadly gauged systems of concepts about the nature of illness and its place in human existence. For example, they explain what disease is, how it comes about, why it exists, what can prevent it or control it or cure it, and why it attacks some people but not others. Human beings seem to have a need to provide explanations for themselves of various kinds of good and ill that befall them. In even the simplest human societies, explanations are advanced and weighed about the reasons for floods, hurricanes, earthquakes, stillbirths, malformations, failed crops, drownings, disease and death. Explanatory models serve to allay anxious fears that accompany otherwise inexplicable events. People are eager to believe themselves in control of natural and supernatural forces rather than the passive victims of some blind and random cosmic process; much of human theory, including science and religion, developed in response to this need. Explanatory models of disease are a part of this body of theory.

Explanatory models have many functions; first, they provide criteria for judging whether or not an individual is really sick. Some cultures find it difficult to accept certain "manifestations" of disease that they cannot comprehend. For some, on the one hand, laboratory results may have little meaning in the absence of pain, fever, malaise or other symptoms. On the other hand, Anglo-Americans do not ordinarily regard recurrent dreams about the dead as a symptom of pathology, as the Navajos do.

A second function of such models is to deal with multiple levels of causality. In other words, a disease model not only provides an explanation for how an illness comes to exist; it also affords a reason why a particular patient happened to fall ill. If the explanatory model is sufficiently complex, it may even provide a list of possible contributory or intervening factors, and ways of warding off or increasing one's resistance to attacks. The three principal levels of causality that are addressed by explanatory models are (1) immediate causes (such as pathogens, malignancies, thrombi), (2) underlying causes (exposure to infection, smoking, atherosclerosis secondary to high blood cholesterol levels) and (3) ultimate causes (genetic susceptibility, bad luck, "stress," insufficient exercise, diet, the "tensions of modern life" and so on).

Cultures differ in the levels of explanation they provide. As one writer has said:

> the distinctive feature of modern science has been the extent of radical delimitation of causal paradigms to immediate causes. . . . Ultimate, purposive causes have been relegated to religion or philosophy as nonscientific issues. Medically, this means that when a patient asks *why* he is ill, he receives an answer about *how* he became ill. Since modern medicine has identified an impressive array of causal sequences, the scientist feels he has provided a satisfactory answer.[5(p132)]

By contrast, members of most non-Western societies deal with other aspects of cause. They want to know why in one child in the same family as another child—eating the same food, sleeping in the same room—leukemia developed, and did not in the sibling. It is in this area of ultimate causes that most of the so-called folk systems of medicine provide explanations, remedies, diagnostic aids and curative measures.

As I noted above, the fact that different medical systems are directed to different levels of cause explains the phenomenon of *medical pluralism*: the fact that a family may happily bring a sick member to a physician's office or clinic for treatment of the "immediate cause," and at the same time be consulting a healer who will search for and deal with the "ultimate cause." In some cultures, it is accepted that an able physician is the obvious choice to reduce a fracture and apply a cast; but only a medicine man can determine why the patient was so out of harmony with his environment that he fell and broke his leg.

Explanatory models deal with larger issues than cause and effect. They may answer questions such as these: Is health merely absence of disease or is it a separate dimension that varies in intensity even in the absence of symptoms? Will ritual purity protect a person from disease? Must one constantly work at staying well, or is health a normal state of homeostasis that will be interrupted only by external malevolent forces? What is the temporal locus of illness? Is an episode of disease something that started happening long ago, perhaps even before the patient was born? Will the asymptomatic present finally emerge as a tardy though inevitable condition? Clearly the answers provided to such questions in various cultures will affect what people do about sickness and health.

Contextual Factors

Many of the articles in this issue deal with various aspects of culturally patterned behavior that are not an integral part of the medical system, but that clearly play a large role in levels of health and the kinds of health problems most often found. For example, cultural patterns in diet, socialization of children, sexual behavior, exercise, the balance of work and rest, ritual observances and many other everyday activities have great import for health status. A substantial literature exists on each of these topics, but they can be dealt with only briefly here. Anderson, Freimer and coworkers, Muecke, Book and associates and others touch on some of these contextual issues.

Emotional Impact and Stigma

While all major disease has emotional consequences for both patient and family, some disease entities have greater impact than others. Cancer is universally feared and dreaded, even in its more treatable forms. In some groups (Native Americans, working-class blacks, Latinos) tuberculosis is a dread disease. Cultural attitudes differ in the face of possible disfigurement, prolonged pain or chronic disability.[6,7] One of the most common

attitudes reported for members of American ethnic minority groups is the degree of stigma attached to mental illness. This stigmatization is related to a tendency to interpret psychological or psychophysiological symptoms as manifestations of somatic disorder alone. Lin, Lock and Brodsky deal with this topic in some detail.

Among Hispanic groups (as reported by Maduro and by Scheper-Hughes and Stewart in this issue) prolonged emotional states are regarded as precursors as well as consequences of disease. In these as well as in other cultures, there is a greater appreciation of the inextricable interrelationships of psychic and somatic phenomena than is common in Anglo-American groups.

The Plan of This Special Issue

In selecting a set of articles for this journal issue, I drew on two principal sources: medical anthropologists who have spent years in most cases studying the cultures and ethnomedical systems of societies that are represented in the United States, particularly in the West. Second, practicing physicians from a variety of specialties in which we have found cultural factors play a major role in eliciting history, establishing diagnosis, obtaining the help and cooperation of family and friends, and convincing patients to follow through with a recommended course of treatment. In some instances, papers have been prepared by teams of physicians, anthropologists and others. In two articles nurse-anthropologists have contributed their special insights.

The first ten articles discuss the ethnomedical backgrounds of nine different cultural groups, ranging from those living in North America long before English-speaking colonists arrived here (Native Americans of Alaska and Hispanic peoples of the Southwest) to the newest arrivals in the United States (the Southeast Asian "boat people" and other Indochinese refugees). In addition to these 9 groups, the final 9 articles deal with two additional ethnic groups, making a total of 11 different ethnic cultures. In order of presentation, these include the following: Pilipinos (Anderson), lower class black Americans (Snow), Japanese-Americans (Lock), Southeast Asian refugees (Muecke), Jamaicans (Mitchell), Pacific Islanders (Fitzpatrick-Nietschmann), Middle Easterners (Lipson and Meleis), Chinese-Americans (Lin), Latinos (Maduro; Scheper-Hughes and Stewart), Soviet Jewish emigrés (Wheat and co-workers) and Alaskan Natives (Dixon and associates; Book and co-workers).

One of the unfortunate omissions in this issue is a discussion of Native American ethnomedicine in the Southwest. Several hoped-for articles did not materialize in time for inclusion here. Readers are referred to excellent articles in the medical anthropological literature on Native Americans, particularly a discussion of Navajo health and medical practices by Kunitz and Levy.[8]

This issue contains clinical and case material from nine medical specialties. These papers, by physicians or anthropologist/physician co-authors are as follows: psychiatry (Lin), geriatrics (Kim), rehabilitation medicine (Brodsky), internal medicine (Wheat and co-workers), obstetrics and gynecology (Minkler), hospital practice (Hartog and Hartog), public health practice (Dixon and associates), nutrition (Freimer and co-workers) and family practice (Berlin and Fowkes).

Sources of Information on Cultural Medicine

There is a growing body of literature in medical anthropology and in cross-cultural medicine to which I would like to refer interested readers. One publication closely related to the theme of this special issue is *Ethnicity and Medical Care,* a volume edited by Alan Harwood.[3] It contains chapters on four American ethnic minority groups that are not discussed in the present collection: Haitian-Americans, Italian-Americans, Navajos (which I have already mentioned), and Mainland Puerto Ricans. The other chapters are on groups represented here (urban black Americans, Chinese-Americans and Mexican-Americans), but those discussions provide different material from those in this issue. Among other collections and general works on ethnicity and medical care are Spector's *Cultural Diversity in Health and Illness*[9] and Spicer's edited volume *Ethnic Medicine in the Southwest.*[10]

Various collections of papers on medical anthropology are readily available. One of the more extensive is Landy's book *Culture, Disease and Healing: Studies in Medical Anthropology.*[11] Other useful collections are by Klein,[12] Leslie,[13] and Logan and Hunt.[14] The medical anthropology text by Foster and Anderson[15] contains helpful discussions and bibliography.

Several journals in the field of medical anthropology are valuable ongoing resources: *Social Science and Medicine, an International Journal* (Pergamon Press, Oxford)—particularly the medical anthropology series edited by Charles Leslie, *Medical Anthropology: Cross-Cultural Studies in Health and Illness* (Redgrave Publishing Company, South Salem, New York), *The Medical Anthropology Quarterly* (Society for Medical Anthropology, Washington, DC), and *Culture, Medicine and Psychiatry* (D. Reidel Publishing Company, Dordrecht, Netherlands). One journal published by the American Sociological Association (Washington, DC), *Journal of Health and Social Behavior,* frequently offers papers on cross-cultural health studies.

Two series of yearbooks devote one or more major review articles of each issue, as a rule, to medical anthropology or cross-cultural medicine. The first of these is the *Annual Review of Anthropology,* whose most recent issue contains reviews by Young[16] and Worsley.[17] The other, a new series, *Advances in Medical Social Science,* has published only a single 1983 volume; the relevant articles are those by Landy[18] and Hughes and Kennedy.[19]

Finally, the medical literature has long contained a sprinkling of papers on ethnicity, cultural variability and medical anthropology, and such reports are increasing in frequency. *The Western Journal of Medicine* for the past several years has been publishing reports

on cross-cultural medicine in a regular section. As Special Guest Editor of this issue, I want to commend Dr Malcolm S. M. Watts for his interest in this topic, and thank him for his encouragement and support.

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Health and Illness in Pilipino Immigrants

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Immigrants from the Philippines and their descendants have tripled in number in the United States in the past 18 years. They will soon surpass 1 million and will be the largest Asian-American minority. Pilipinos in the United States are diverse ethnolinguistically and in important socioeconomic and demographic dimensions, one notable feature being the high level of education and professional status of many recent immigrants. Nevertheless, the health and disease circumstances of Pilipinos and their views of health and illness have been surprisingly neglected to date. A generic principle fundamental to their view of health is that concerning the maintenance of balance. Proper social and cultural conduct is believed to help avoid health problems. Imbalances in social relations, infringements of cultural norms or adverse interaction with the supernatural are linked, in the cultural logic of Pilipinos, to illness.

Populations from what became known as the Philippines have long been famous for their willingness to undertake international migration. Tomé Pires[1] reported their presence as mercenaries in Sumatra and as miners and traders in the Malay Peninsula in 1511. Modern Pilipino* immigrants have overwhelmingly chosen the western United States (73% reside here) to pursue their ambitions, though equal numbers have now migrated also to the Middle East and Europe for employment. So spectacular has the flow of Pilipino immigration to the US been, particularly since 1966, that by 1985 they will be the largest group of Asian-Americans. Numbering 774,640 in the 1980 census, Pilipino-Americans surpassed Japanese-Americans and trailed Chinese-Americans by less than 35,000.

It comes as some surprise therefore that so little attention has been given and so little information exists concerning Pilipino-Americans.[2] Many reasons for this neglect will become evident as our depiction of Pilipinos unfolds, but undoubtedly their status as one-time colonial subjects of the United States, their rapid and recent rise to ethnic prominence and, lately, their relatively smooth integration into US society have in some measure deflected serious consideration. Another deterrent may lie in the great difficulty in generalizing about Pilipinos, so heterogenous are they in terms of subethnic background, education, occupation, income and distribution.

At this writing Pilipinos are the largest population of Asian-Americans in the western states as a whole. First among Asian-Americans in California (357,514 or 1.5% of this state's people) and Alaska (3,095 or 0.8%), they are second (to Japanese-Americans) in Hawaii (133,964 or 14%) and Washington (24,363 or 0.6%) and are third in the remaining western and mountain states except Nevada. In Nevada, Pilipinos represent the largest Asian-American population although comprising only 0.5% of the state's population. In other mountain states they constitute only 0.1% of the population. In Oregon they make up 0.2%. Nearly as dramatic has been the more than doubling of the number of Pilipinos in each of the western and mountain states during the past decade. This is a total increase of 285,162, or 113%.[3]

In this article I will synthesize relevant information for practicing physicians concerning the culture of health of the Pilipino ethnic group, drawn from the available literature as well as from my long-standing anthropologic research in the Philippines and long interaction with members of the Pilipino community, especially in the San Francisco Bay Area. The wide range of documentary sources is, as might be expected, of uneven quality as well as quantity. Special effort is made to cite the most relevant and most recent literature. Numerous gaps in information exist concerning the health status and problems of Pilipinos. Especially disconcerting is

* Throughout this article *Pilipino* is used to refer to persons of Philippine ancestry. Pilipino has recently come to be preferred over Filipino by immigrants to the United States for purposes of ethnic identity, in line with the usage adopted by the national language of the Philippines (which does not have the letter "f").

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the lack of data on mortality and morbidity and an absence of comprehensive treatment of health problems associated specifically with the ethnic group. It is hoped that readers will be moved to conduct research on this important yet neglected minority.

Ethnic Identity, Demographic Profile and Migration History

Certain characteristics of Pilipino immigrants to the United States are relevant to our purposes. Pilipinos abroad tend to view themselves as a single people more than they do in the Philippines. There the divisions between Christians, Muslims and minorities (mainly Chinese and upland peoples) and between ethnolinguistic groups of Christian Pilipinos continue to influence stereotyped social distinctions. Immigrants to the United States are predominantly Christian, mostly Catholics who can speak the national language and most are from a few subethnic groups. Yet it is vital to recognize that significant differences fragment them.[4]

The most important of these differences can, for purposes of simplicity, be represented in a distinction between early and recent immigrants.[5,6] In certain respects these constitute two distinct populations. Most immigrants in the earlier part of this century (1905 to 1935) were male laborers of rural origin, speaking only their local dialects, with the result that their noneconomic participation in US society was limited. By contrast, immigrants since 1966 (with the initiation of PL 89-236) have been mostly well-educated, English-speaking urbanites. An unusually high proportion of them are professionals.[7] Many of the recent immigrants came as families and most are young (between 20 and 40 years). The rapidly aging "old timers" often still reside in rural communities whereas the huge wave of recent immigrants has almost all settled in urban and suburban areas. In Hawaii, earlier immigrants continue to occupy the lower strata of economic and social life. These differences, particularly the differentiation by income and class and between Hawaiians and mainlanders, are strongly associated with differential participation in the political, economic and social systems. The new immigrants have drastically altered the demographic and social organization of Pilipinos in the United States. The wave has by no means crested; the search for opportunities and the oppression and stagnation of the present Philippine government and economy continue to drive emigration.

The proportion of Pilipinos born in the United States (the latest census figure for 1970 was 43%) increases slowly, despite the enormous continuing immigration because of relatively high fertility. US-born (largely second or third generation) and foreign-born Pilipinos also differ in certain respects socially and culturally, although these differences are gradually disappearing. The youth of both groups results in a young total population in spite of the large number of early immigrant male "old timers." Also, between US-born and recently immigrated Pilipinos, the previously drastically unbalanced sex ratio is now essentially balanced.

Residence of Pilipino immigrants, which is presently only about 5% rural, has tended to be ethnically concentrated in certain suburban communities. At present they show a greater willingness to live scattered in suburbs.

Professionals, Especially Health Professionals, Among Immigrants

Since 1966 the proportion of professional, technical and kindred workers—PTK, a designation of the Immigration and Naturalization Service—has averaged a remarkable one third of the total number of immigrants from the Philippines. This category among Pilipinos includes physicians and surgeons, dentists, nurses, pharmacists, lawyers, engineers, teachers and accountants most prominently. Mejia and co-workers state that "In absolute numbers the Philippines is the world's largest donor of physicians after India."[8(p57)] A significant number had arrived in the United States before 1966 but after that date the number increased four to five times. By 1974, 10,410 Philippine physicians had entered the United States, or one in eight of the non-US-born medical graduates. Of Pilipino medical graduates, 90% remain here as permanent residents or citizens. Most striking perhaps is the fact that a third of these are women, but also striking is the youth of entering Philippine-born physicians. In the mid 1970s a high proportion were staff physicians or residents, only about 23% being office-based. For reasons of ease of communication, most Pilipinos prefer to be attended by Pilipino physicians but the relatively small proportion in private practice means that most see non-Pilipino doctors.

As with physicians, the licensing of nurses in the US has increased significantly since 1966. By 1972 Pilipinos constituted nearly half of all foreign-born nurses. They tended to be young (between 23 and 32 years), female, unmarried and self-supporting, according to Joyce and Hunt.[9] Those few (about 9%) among their sample who returned to the Philippines were significantly older, were married with families in the Philippines and were employed by, or scholars of, the government.[8] About 16% of the sample of Pilipino nurses studied by Mejia and associates married non-Pilipino Americans. In general, Pilipinos are probably less adverse to marrying non-Pilipino Americans than are other Asian-Americans, another factor in their relatively rapid assimilation.

The number of dentists from the Philippines, although miniscule when compared with that of physicians and nurses, nonetheless represents almost 44% of Asian-born dentists entering the United States. Likewise, Philippine-born pharmacists represented 44% of Asian immigrant pharmacists during the decade ending in 1974 (Annual Report, Immigration and Naturalization Service, US Dept of Justice, 1974). In both categories women are especially highly represented.

Including all categories of professional and technical occupations, Pilipinos of the recent wave possess educational qualifications that render them professionally

competitive. Because of their number, however, and given prevailing adverse economic conditions, many have encountered difficulties entering jobs commensurate with their training. In particular, Pilipinos have encountered licensing problems and alleged differential treatment. This has been particularly the case among nurses, dentists and pharmacists, though physicians have not been unaffected, and this has generated a certain amount of bitterness.[10]

Biological Makeup and Genetically Derived Predispositions

The genetic background of Pilipinos and the possible disease implications related to this background are poorly documented. This situation contrasts sharply with that for persons of Chinese or Japanese ancestry. The biological makeup of Pilipinos is certainly very complex. Older strata of modern populations entering the Philippines at least 40,000 years ago were relatively isolated demes on the major islands until about 4,000 years ago when seafaring dramatically reestablished the movement of peoples throughout Southeast Asia[11] and reintroduced the biological variation that existed among prehistoric populations of that region. Over the past 2,000 years gene flow, especially from southern Chinese and, later and more limited, European sources, further hybridized the dominantly "Malay" gene pool with its strong southern Mongoloid influence. Thus, Pilipinos are genetically highly mixed. Phenotypically they are quite similar to and sometimes mistaken for other Southeast Asian peoples or southern Chinese, especially those who have some Chinese ancestry. Although good serologic and antigenic analysis of Pilipinos is quite limited despite aforementioned variation, in general they are characterized by blood group B (about 40%), Diego factor, a low incidence of Rh negative, a high incidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, a relatively high incidence of α-thalassemia[12] and apparently a high incidence of genes responsible for lactose intolerance and malabsorption.*

Survey of Selected Health Problems

Comprehensive information is lacking concerning the health status and problems of Pilipinos in the United States. Again it compares poorly with that available for Chinese and Japanese populations. As already indicated biological and sociodemographic variations among Pilipinos are noteworthy. These variations and limitations of the literature make generalizing somewhat perilous. Available information focuses principally on Pilipinos in Hawaii with its older and until recently, largely male and dominantly rural population. Disease problems dealt with are mainly the diseases of civilization, especially "Western diseases"[13] such as coronary heart disease, hypertension, cancer of the bowel, lung and breast, renal stones and hyperuricemia and gout. The following are recent studies that have built on earlier work.

Gerber studied, in Pilipinos who arrived in Hawaii before 1931, mortality that was attributed primarily to coronary heart disease. Mostly men from the Ilokos provinces, their age-specific (55 to 64 years) death rates from coronary heart disease were 61% higher than those in the Philippines and were intermediate (249/100,000) between Hawaiians of white and Japanese ancestry. Death rates were significantly higher for urban (468/100,000) than rural (355/100,000) Pilipinos and were higher for residents of Oahu than for Maui and Hawaii. Most notable was the increase in the mortality from coronary heart disease by 2.6 times between 1950 and 1970 (rates for women increased 1.4 times). Gerber attributes this rapid increase in mortality from coronary heart disease mainly to a dramatic change in life-style among Hawaiian Pilipinos.

In a study by Bennett and associates,[15] a relatively high incidence of hypertension and cerebrovascular accidents was identified among Hawaiian Pilipino men. In the same study an unusually high incidence of both conditions and of renal disease was noted among Pilipino women. Bennett[16] later showed that Pilipinos had the highest incidence among five ethnic groups of hypertension, peptic ulcer and impairments of back or spine and the lowest incidence of asthma and hay fever.

Hinds and colleagues[17] reviewed cancer rates among Hawaiian ethnic groups and attempted to link them with smoking and alcohol use. Cancer incidence rates for Pilipino men were found to be relatively high for liver and biliary system cancer (38/100,000) and for lymphoma (28/100,000), moderate for cancer of tongue and mouth, pharynx, esophagus, rectum, pancreas and bladder and leukemia and low for cancer of larynx, stomach, colon, kidney, lung and brain relative to other ethnic groups. Women were found to have moderate incidence rates for tongue and mouth, stomach and lymphoma cancer and leukemia and low for other types of cancer enumerated. Overall, Pilipinos recorded the lowest incidence of all ethnic groups in Hawaii. In another study, Kolonel and co-workers[18] attempted to relate cancer of the colon, rectum, stomach, prostate and breast with dietary causes, especially fat intake. Hawaiian Pilipinos who have among the lowest risk of cancer of the colon and prostate for men and for colon and breast for women were found to have the lowest fat intakes.

Glober and Stemmermann[19] provide a useful summary of the disease concomitants of westernization among the ethnic groups of Hawaii. In 1970 Pilipinos remained the least acculturated ethnic group, having the lowest median family income ($12,683), the highest proportion of laborers (45%) and the lowest proportion of professional, technical and managerial occupations (10%). They (women especially) ingested the lowest levels of total protein, animal protein, saturated and unsaturated fats and meat nitrites of any population. As already indicated, they had the lowest rates for all types of cancer by a significant margin, this being

* Dr Kaichii Omoto of the Department of Anthropology, Faculty of Science, Tokyo University, has in recent years been conducting extensive studies of antigen frequencies among Pilipino and Southeast Asian populations. His work as it comes to publication will rectify some of the present gaps in our knowledge.

especially notable for women. According to Glober and Stemmermann, however, there is a "tendency for tumours which are common in the host country to increase among the immigrants" and for "cancer rates, which increase or decrease after immigration [to] change more quickly in men than in women."[19(p324)] For the past two decades, many Pilipinos in Hawaii have experienced a dramatic improvement in socioeconomic status and a shift to urban life. It would be most appropriate to undertake research to determine whether as with the spectacular increase in mortality from coronary heart disease experienced between 1950 and 1970, an increased incidence of certain tumors is also occurring.

In studies of Pilipinos in Seattle and in Hawaii, Healey and associates[20] reported cases of hyperuricemia (6.3 and 6.1 mg per dl, respectively) and a high incidence of gouty arthritis. These findings relate the increased incidence to probable higher intakes of protein and purines by immigrant Pilipinos in the United States and suggest that some Pilipinos may have a genetic incapacity (perhaps due to a heritable renal tubular defect) to handle higher purine loads found in their changed diets.

It is clear from the foregoing that there is a pressing need for biomedical and epidemiologic research among Pilipinos, especially among the large, recently immigrated mainland population. This is an especially timely moment to pursue a wide range of biomedically interesting questions.

Mental Health

Of the psychopathologies attributed to Pilipinos in Hawaii, schizophrenia has received the most attention.[21-23] Weiner and Marvit[24] found a moderate incidence (2.5/1,000) as compared with other ethnic groups. In their sample, Pilipinos showed a somewhat later age at diagnosis than other groups (about 43 for male and 36 for female patients) and an unusually high mortality ratio (2:7 for females). In earlier studies of admission records of Queen's Medical Center (Honolulu), Wedge and Abe[25] found Pilipinos slightly underrepresented according to their number in the population at large. Those Pilipinos admitted had diagnosis of having a high frequency of what they called "major reactions," schizophrenia and manic-depressive and involutional psychoses.[26]

In studies of the cultural expression of paranoid schizophrenia in Pilipino and Japanese male immigrants in Hawaii, Enright and Jaeckle[27] and Bloom and colleagues[21,22] found that Pilipinos were characterized by greater violence, more bizarre behavior and more dramatic delusions of persecution and of grandeur. Pilipino patients "tend to express feelings freely and directly" and to attempt to resolve conflicts by directing their behavior outward to alter circumstances.[27(p17)] In a brief but suggestive paper based on 51 admissions of recent immigrants to Langley Porter Neuropsychiatric Institute (San Francisco) from 1968 to 1972, Shon[28] reports a higher proportion of women and of Philippine-born admitted (57%). Only 43% had diagnosis of psychosis, mainly schizophrenia, although some doubt existed whether many of these patients were truly schizophrenic or "rather were suffering from a transient situational disturbance (adjustment reaction)."[28(p16)] What is especially interesting is that "in most cases a precipitating event involving loss of self-esteem was present, e.g. failing a licensure exam, a professional unable to obtain a position in her field and forced to take a menial job, or a wife discovering her husband was dating other women."[28(p16)] "In almost every history of diagnosed psychosis there was a strong association with a recent event involving great loss of self-esteem, loss of status and shame."[28(p15)]

Marsella and co-workers[29,30] correlated emotional stress among married, male Hawaiian Pilipinos, who varied by class and age, with manifestations of psychologic symptoms. Social and emotional stress was associated by them especially with familial and interpersonal relations of responsibility and obligation, with an oppressive assertion of authority and with being criticized. Lower-class men were found to be more severely socially stressed than upper-class persons.

Studies by Sechrest[31-33] suggest that the symptomatology of psychiatric patients in the Philippines frequently involves violence, disturbance of sleep, wandering about aimlessly, socially inappropriate behavior and insensible utterances (also L. Sechrest, MD, unpublished data, 1966). He notes a very low frequency of symptoms of withdrawal, depression and suicide.[31(pp197-198)]* Complaints of patients mainly involved hallucinations, a significant proportion being visual and concerned with a threatening or commanding figure.[33] The delusions of Pilipino women involve power and authority figures and especially sex and imaginary suitors.[31,32] Paranoia is prominent for both sexes.†

Sechrest associates first- and second-parity siblings and last-parity women from small families with psychotic disorders (principally schizophrenia). He relates this to the extreme social expectation on them for responsibility. Shon[28] makes an almost identical finding. He also stresses the stigma that especially unacculturated Pilipinos attach to psychopathologies, which are generally believed to be hereditary. Thus home care by a family keeps many of the less violent

*Enright and Jaeckle[27] found similar symptom complexes among Pilipinos in Hawaii that contrasted sharply with their Hawaiian-Japanese sample. In a brief report on paranoid schizophrenia, Bloom and colleagues[21] listed symptoms common to Pilipinos such as delusions, auditory hallucinations, delusions of possession of great powers, homicidal feelings, hearing threatening voices, unmanageability, violence, possessing weapons, "being God" and "talking with God." Commenting on differences from Japanese, they state that Pilipinos diagnosed to have paranoid schizophrenia "show almost unadulterated externalizing, both behaviorally and ideationally. They are turning their anger outward physically, and their grandiosity is the highest theoretically possible!" Ibrahim and associates[34] confirm the low rate of suicide among Pilipinos in Hawaii but note that the rate is increasing for men, though remaining unchanged for women.

†Similar findings are reported by Duff and Arthur[36] who, in a perceptive paper on the clinical features of hypochondriasis and paranoia among Pilipinos in the US Navy, suggest they are "faced with acculturation problems while doing servile work and maintaining close ties to home [and strong responsibilities]. Some incident or life crisis, such as the arrival of a new and tyrannical chief petty officer, perhaps some physical illness such as influenza, might prevent the individual from fulfilling his obligations. This failure to meet obligations and to attain his goals might give rise to feelings of inadequacy, impotence and . . . shame accompanied by anxiety." Their cultural background "discourages open expressions of anger and boldness as well as individual initiative . . . [predisposing them] to . . . a classic passive method of handling feelings of inadequacy namely, somatic complaint or hypochondriasis."[36(pp208-209)]

or seriously disturbed cases out of clinics and institutions. This, plus a great respect for elders, probably explains the very low incidence of diagnosis and admission for senile dementia, mental retardation and perhaps psychotically depressed states among Pilipinos. Finally, Sechrest[31] and Sechrest and Flores[37] have noted that conflicts about homosexuality are rarer in the Philippines than in the United States (see also Hart[38]).

Lapuz[39,40] provides a fascinating picture of cases of neurosis and psychosis in persons from urban upper and middle classes and the cultural context of these disorders in the Philippines. Her sample shows a high proportion of bizarre somatic symptoms for which an organic cause could not be identified. She also found a relatively high frequency of suppressed depression[39] and a frequently expressed fear of loss of control and similar phobias that arose to prevent loss of control. Lapuz's patients, especially the women, show highly aggressive tendencies but, according to her, they are usually able to express their aggression in socially acceptable ways. Pilipinos are quite remarkable in their ability by means of key sociocultural practices to maintain a proper front, to protect their self-image, to express concern for others' feelings and to get along with others, avoiding embarrassment or confrontation. Yet when repressed aggression builds up it often erupts violently. Kimmich describes Pilipino patients in Hawaii in a closely comparable way.[26]

Culture, Health and Illness

Turning now to indigenous conceptions of health and illness, I will review those health problems that are primarily shaped by culture.* We must begin by reemphasizing the caution that subethnic variations exist in the specific expression of beliefs and behaviors. It is impossible to generalize about a common Pilipino culture; yet, because variations are limited and until specific ethnic variants, which themselves are rapidly responding to change, are better defined, we can for present purposes describe certain gross commonalities. Having said that, clinicians are strongly advised to include in history taking where their Pilipino patients come from (or, in the case of US-born subjects, where their parents [grandparents] come from), when they came to the United States and their occupation, education and religion. Pilipinos show highly individualistic behavior and are very responsive to situational conditions. Thus, their adherence to ethnic behavior may vary not only by degree but according to specific circumstances. Whereas many Pilipinos may appear to be "Americanized," it must be stressed that some of this is in fact quite superficial. Even urbane professionals who apparently are fully acculturated will exhibit the profound influence of their cultural roots at unexpected times.

Pilipinos, who benefited appreciably from the legacy of the excellent public health apparatus established during the American colonial period, are very receptive to modern medicine. Yet they have not relinquished a large body of indigenous disease theories and health practices. Pilipinos who tend to differentiate dramatically between formal and informal behavior do so with respect to biomedical knowledge and in their interaction with health professionals and health services. On a formal level there is (apparent) sophistication. On an informal level adherence to indigenous conceptions of health and illness may strongly influence health care, patient compliance, resort to alternative sources of care and management of culturally specific syndromes.

The Principle of Balance *(Timbang)*

The most central indigenous Pilipino health concept is that of balance. Health is a result of balance, illness is usually the result of some imbalance. Actually a much more complicated system, it appears simple because it is based on a few fundamental principles. One of these is the range of "hot"-"cold" beliefs concerning principally humoral balances in the body and food and dietary balances.[44] According to the theory, rapid shifts especially from "hot" to "cold" cause illness and disorders. Optimal health is maintained in part by maintaining a "warm" condition. Pilipinos avoid cold drinks or cooling foods the first thing in the morning because these are thought to cause cramps in the diaphragm *(masisikmura)* or when a body is considered overheated and thereby vulnerable, as during a fever or following childbirth. Carrying the logic of the system one step further the body and muscles can become distressed when they are suddenly cooled. Thus, for example, after ironing one should wait a while before bathing or even washing hands in cold water, otherwise pain will develop in an arm so overheated. As with maintaining "warmth," being a little "stout" and especially keeping baby fat are preferred to being too thin —for added protection or a reserve in one's vital strength.

Another belief that correlates with heating and cooling concerns the quality and balance of air (*hangin,* "winds") in the body. The entry of cold air via drafts is especially upsetting to the system. Wind does not actually have to "enter"; just blowing on a body may induce colds, fever, rheumatism, pneumonia and other respiratory tract illnesses. Similarly, sudden changes in the weather, seasonal changes brought on by the onset or reversal of monsoons, strong winds, cool breezes or exposure to low nighttime temperatures, vapors rising from the earth, appearances of very hot sun after a lengthy rain and so on are believed to upset the balance of the body. Overheating or rising vapors not only cause fever or pains but can also cause disorientation. For example, if children play in shade (worse if directly in the sun) when vapors are rising

*Harwood[41] provides an excellent general treatment of the relationships of ethnicity and medical care and fine case studies of seven ethnic groups. Unfortunately, Pilipinos are not included in that volume, but it is still worthy of a clinician's attention. My synthetic version of Pilipino health beliefs and practices in this paper derives from my long-standing research among Pangasinan and Ilokano rural and urban populations as well as from available comparative literature. Especially valuable is the work of Hart[42] and Lieban.[43]

from the soil due to evaporation, they get aches in the joints called *rayuma*—"rheumatism" being a catch-all for muscle and joint pains. What is more dangerous is that it may cause children to become disoriented. This is expressed in confusion and incoherence, which are indications that the soul has wandered from the body. Calling a child's name repeatedly may bring the child's soul back; if not, a practitioner is consulted who knows how to find the soul. "Wind" entering the body when it is "open" and thereby especially vulnerable, such as after childbirth, during an operation or when suffering from fevers, is extremely dangerous. Thus, most of the elaborate prescriptions and prohibitions concerning "mother roasting" and infant care[44] are to protect the body from cooling air. Wind can also be produced in the body by certain foods and drinks, thereby causing distress.

Pilipinos place a very high value on personal cleanliness. Keeping oneself clean smelling and clean looking in body, clothing and personal effects is as much for health's sake as it is for clean appearance or "face" sake.* To be slovenly and disorderly *(burara)* is to be shamelessly irresponsible. Bathing and washing after voiding help maintain health. Morning and evening (if not more frequent) baths are taken for pleasure and for the maintenance of the proper hot-cold balance of the body. Although baths are prescribed under certain circumstances, it is believed that irregular or infrequent bathing can lead to illness. Baths of warm or cool water, often medicated with herbs, are prescribed therapeutically to restore imbalances.

Imbalances that threaten health can be brought about by personal disorderliness and by irregularity more generally. Pilipinos believe that we get pretty much what we deserve—that is, everything balances out. If someone is disorderly, undisciplined, sinful or antisocial, that person or perhaps members of the person's immediate family will pay for it by illness, accident or other misfortune. Guilt has little influence on Pilipinos. Much stronger is the belief that what someone does will come back, perhaps through divine retribution. Also, irregularity in sleeping, eating and bodily functions can cause problems and thus are to be avoided if possible. Of great concern to menstruating women is not only that their monthly period occur on schedule but that it have the proper volume. Herbs or prescribed foods are often taken to insure or rectify an adequate flow.

Imbalances leading to illness are considered to be caused by certain other circumstances. For instance the onset of social or emotional stress, worry, anxiety, grief or a loss of self-esteem can cause or contribute to a loss of equilibrium and thereby a susceptibility to diseases or disorders.[45] Unsettling experiences—being startled, awaking suddenly from deep sleep, bad dreams or terror—can also lead to disequilibrium. The uniquely Pilipino-Malay culture-bound syndromes, *mali-mali* (or *uto-uto,* a startle reaction accompanied by echolalia, echopraxia, coprolalia and command automatism), *amok* (a state of unrestrained violence and murderous frenzy),[45] *lanti* (sudden fright among infants and children),[46] *bangugut* (sudden death),[47] *pasino* (a frequent precursor of mental disorders)[33] and soul loss all fall into the category of loss of equilibrium.

The Pilipino folk beliefs described so far fall under what Foster has called *naturalistic* principles "which explain illness in impersonal, systemic terms," in which "health confers to an *equilibrium* model."[48(p775)] Although not mutually exclusive, on the other side of the coin are *personalistic* principles that explain illness by referring to the "*active, purposeful intervention* of an *agent* who may be human (a witch or sorcerer), nonhuman (a ghost, an ancestor, an evil spirit) or supernatural (a deity or other very powerful being)."[48(p775)] Hart[42] suggests that the belief system that he studied in Samar is primarily personalistic. The system with which I am familiar in Pangasinan, including explaining diseases by principles of modern medicine, is today more naturalistic than personalistic in emphasis.

Among Pilipinos those personalistic agents that are understood to cause illness fit quite congenially within the broad conceptualization of balance. For instance, sorcery induces an imbalance involving the "planting" of damaging objects in the body or poisoning. At least potentially these physical attacks can be treated by a shaman who extracts the object or uses counter sorcery.[49,50] Disorders believed caused by vengeance of spirits or souls because of unintended intrusions in the lives of "unseen" environmental spirits or by inattention to rituals to the memory of recently deceased create disequilibrium. Vengeance in the case of the latter may even involve possession. To reestablish balance, spirits or souls must be placated with rituals involving feasts or they must be exorcised.

Sociocultural Premises of Health and Illness

Pilipino conceptualizations of health and illness and those for the conduct of sociocultural relations are logically highly coherent. The cognitive system just sketched was characterized as very simple, and indeed it is. By contrast, health and illness behavior is extremely complex and difficult to classify. This is because illness behavior is closely linked with social behavior, being particularistic, personalistic and situational. Put differently, the concepts used by Pilipinos to understand the nature, cause and treatment of illness, both physical and mental, are consistent with and informed by those that order their social behavior. The root metaphor of "balance" in health and religion is expressed in the key value of reciprocity in social interaction.[51]

Pilipinos place a very high value on proper social conduct. The ideal is a refined person who manages smooth interpersonal relations, acknowledges debts

* Philippine languages contain an elaborate vocabulary of smells and of words referring to the distinctive smells associated with various parts of the body. This cultural linguistic elaboration suggests the great concern for remaining clean smelling.

of gratitude, behaves appropriately in various situations, shows proper consideration of others, anticipates their needs, displays sensitivity in social interactions and uses pleasant and correct language. An ideal person also avoids shame and avoids stating unpleasantries or confronting others when in face-to-face interactions. Generally avoiding discourtesy, a correct Pilipino uses euphemisms and go-betweens, possesses a strong sense of self-esteem but is respectful to authorities, knows his or her place and is fiercely loyal to intimates. In all of this, it is the form that counts, the emphasis being on propriety, social skills and maintaining an ideal image of reality. But a vast difference often separates professed, ideal behavior and actual behavior and separates face-to-face and non-face-to-face behavior. Actual behavior often involves a striving for power, status and wealth, self-assertion, egocentrism, instrumental behavior, avoidance of responsibility and tactical flexibility. This is the assertive, individualistic side of Pilipinos, which cannot adequately be discussed here. An aggressive competitive person who fails to observe expected behavior and proper etiquette and is insensitive to others' feelings or needs is at great risk of being shamed. Finally, if on the formal level the specific rules of etiquette and proper behavior are precisely known, behavior at the actual, informal level must be flexible to accommodate to specific situations. Here ambiguity and indefiniteness are the rule and a person at any particular time has a wide range of behavioral options.[53-56] In this ambiguity problems can occur.

Methods of Socialization

Children are reared in a highly protective environment and are indulged shamelessly until about age 6.[41,56-60] Socialization is as much for learning and practicing social interaction skills and social sensitivity as it is for learning the specific, highly situational and complex rules of behavior. The process emphasizes negative sanctions rather than positive rewards, by means of frightening, teasing and shaming to achieve avoidance of possible misconduct. Children are taught to be quiet, to avoid direct confrontations about personal differences, to contain their emotions and to be obedient, respectful and shy. Children are prepared to face as adults what is perceived as a hostile world of dangerous human and nonhuman (spirits and ghosts) elements ready to take advantage or to do them harm. Children must learn safe places (home and neighborhood) and safe people (family, neighbors, kin and friends) and avoid dangerous places (the unknown outside world) and people (strangers). The effect is to reinforce internal controls and to discourage persons from trying to change their place—thus upsetting social equilibrium—by leaving their comfortable cocoon of kith and kin and friendly spirits and ghosts for the dangerous outside world and better life chances. Socialization is thus predicated on recognition and avoidance of dangerous situations and on constraint of expressions of aggressiveness toward others or toward one's environment. The price of safety within the family and close kin is accepting dependence, obedience, submission and withdrawal. In the outside world of strangers, the formal etiquette of proper social conduct is one's best protection against exploitation, harm and shame. In short, the major values of ideal social behavior are acquired through practicing avoiding shame. Social and personal reward and well-being result from avoidance of pain, criticism and embarrassment, and thus the disequilibrium that usually results from inappropriate behavior. "A person is viewed as being in a perpetual struggle to maintain an equilibrium between conflicting forces within the environment and one's social relations."[55(p278)]

Impairment of Health

Health is viewed as a positive state or, more specifically, a process that one maintains by avoiding circumstances that could result in illness. Health is impaired in the following ways:

- By natural causes such as heredity, pathogens or poisons, traumas and imbalances of hot and cold, wind or blood.
- By inappropriate behavior, criticism, shame, conflict or violence, as well as social irresponsibility, which induces stresses and imbalances that reduce a body's vital strength and vigor and thus puts one at risk for illness, either physical or mental[29,61] (this vital force can be enhanced by social control, proper social conduct and higher social status).
- By social punishment for improper or unethical behavior toward others by means of sorcery[19] or divine retribution.
- By supernatural causes that are often initiated by inappropriate behavior toward unseen spirits, the recently dead or revengeful ghosts (negative reciprocity) by possessing or by wreaking magical vengeance on an offending person.

Pilipinos often do not respond to illnesses until they have become quite advanced and the patient has taken to bed, is suffering severe pain or falls unconscious.[62] They often explain their delay in responding seriously by suggesting that they were watching the progress of the illness for indications of what it is. That is, they were trying to identify its particular defining characteristics, possible cause, severity, chronicity and threat to others. Those are the indicators by which the family, neighbors or an indigenous diagnostician decides to whom they should go for treatment.

The previously mentioned culture-bound syndromes can be understood as cultural loopholes—that is, as conventionalized, legitimized responses of the sociocultural system. These cultural loopholes are exercised when no other solution is possible. Thus, specific cultural expressions in illness, in culture-bound syndromes or in mental disorders are simply outcomes of sometimes excessive attempts to follow conventional Pilipino behavioral pathways.

The basic logic of health and illness involves both

prevention (avoidance of inappropriate behavior that causes imbalance) and curing (by restoring balance). Paralleling this comprehensive indigenous belief system is the understanding that certain diseases and disorders are best treated by modern clinical medicine. These are understood as operating by a different logic. What is of interest is how little conflict is perceived between these two explanations in Pilipino cognition. If most conditions in their present cultural environments are best treated by physicians and surgeons, others are also best treated by home remedies, folk practitioners and faith healers. Certain conditions it is believed will only be worsened by modern clinical treatment. Coexistence of the two systems is likely to continue. Pilipinos do not sharply distinguish between the material world of the living and the supernatural world of natural spirits and ancestor ghosts. Early learning and constant reinforcement perpetuate belief in the manifold world of spirits. Their existence and human frailties and faults support the continuing practice of folk diagnosticians and healers who can placate or exorcise spirits and ghosts. Women play an especially notable role in illness diagnosis and treatment, often serving as folk curers.[49]

Limitations of space preclude further discussion of the forms and functions of Pilipino practitioners here. Excellent depictions can be readily consulted for rural folk curers and diagnosticians[33,42,59,62-67] and for urban practices.[33,43,49,65,68,69] They are also active in Hawaii[70] and on the mainland.[71] Folk practitioners are sometimes sought out first because they are kin, neighbors, friends or friends of friends. This personalistic link provides a basis for trust, which for Pilipinos is not infrequently preferred over impersonal expertise. Preference for folk practitioners is also based on a belief in their effectiveness for specific conditions, their low cost and the ease of communication one feels with them. This value of personalism, demonstration of personal concern and effort to enter into genuine communication should not be ignored by clinicians. It explains why Pilipino patients prefer Pilipino physicians. It may be in part responsible, along with the value of "making sure" when a situation is ambiguous, for the not uncommon practice of Pilipinos to receive treatment from a clinician and a folk healer at the same time,[68,69] perhaps following multiple prescriptions including drugs. Clinicians should anticipate this possibility. They must also be alert to a tendency for self-medication and the use of powerful medicinal herbs and prescription drugs (both are easily obtained and casually taken in the Philippines).

Problems in Encounters With Health Professionals

Some additional interactional problems may appear in a therapeutic encounter. Pilipinos, especially recent immigrants (those mainly encountered today), appear so sophisticated and speak such good English that it is easy to assume that communication difficulties are few. This is not necessarily the case, as Maslog[72] reports. There may also be adverse effects from communicating to a patient (though not to the patient's family) bluntly and in an impersonal, technical way the full extent of the person's disease or disorder. As we have seen, sudden shock that raises anxieties in a patient whose vital strength is already reduced may worsen a situation. The role of the family and the wider group of loved ones and friends is obviously of fundamental importance to Pilipinos. Separation from family, loneliness and incurring shame to the family can all create or exacerbate illness behavior. Family visits and assistance in hospital and early return to the home can often prove salutary for in-hospital patients. The inclusion of family members or other companions during history taking may also prove beneficial during clinic visits. Pilipino patients tend to be reserved and overly compliant in a situation in which they are already "out of balance" and in the presence of an authority (the clinician). Third-party companions can often enhance communication. It is usually well worth the extra effort on the part of office staff or physician to include them, for it may enhance adherence to the prescribed biomedical treatment regimen.

Summary

Having been successful immigrants for so long to so many different places and having been colonized for almost 400 years, Pilipinos have become remarkably adaptable. This quality has been achieved by clinging to a few fundamental social institutions and cultural premises. They have, despite continuous stimulus, been able to retain what they considered central and important, giving up mostly those elements that for them are more peripheral in nature. Much like the old French adage, the more Pilipinos change, the more they remain the same. I hope this article has contributed to greater awareness and sensitivity to Pilipino patients and their culture on the part of clinicians.

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Traditional Health Beliefs and Practices Among Lower Class Black Americans

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The medical belief system of lower class black Americans reflects their social, political and economic marginality in the larger society. A moderate life-style is regarded as the basis for good health with special emphasis on protecting one's body from cold, keeping it clean inside and out and maintaining a proper diet. Illnesses and other life events are classified as "natural" or "unnatural." Natural illnesses result from the effects of cold, dirt and improper diet on the body causing changes in the blood. A number of beliefs about blood and its functions have important clinical implications for the treatment of hypertension and venereal disease and for family planning. Natural illnesses also result from divine punishment and serve as an instrument of social control. Unnatural illnesses are the result of witchcraft and reflect conflict in the social network. It is believed that physicians do not understand and cannot effectively treat such illnesses, but a variety of traditional healers offer help to the victims. Physicians must elicit such beliefs if they are to interact effectively and sensitively with black patients. Social change is required, however, to eliminate the feelings of powerlessness at the root of many of the health problems of poor black Americans.

> *These white folks don' care nothin' 'bout you and me and they don' want to see us flerishin'. That's why so much of that medicine they always after us 'bout takin' is agains' us. These doctors ain' nothin' but white folks, too.*[1(p220)]

These words, spoken by a 78-year-old black woman to a black anthropologist, underscore a point made in an essay about the health beliefs and practices of American ethnic groups.[2] Chrisman and Kleinman state that members of such groups who "come into contact with orthodox medicine that differs significantly from their traditional practices will often react by ignoring the treatment prescribed, or misusing it, or complaining about the quality of the care they are getting."[2] The results, they note, are generally poor. Traditional medical systems frequently contain a supernatural, magical and moral component in explanations for and management of sickness, a component largely missing in the more secular and increasingly more technical arena of biomedicine. This disparity between lay and professional explanations of health and sickness, further widened by barriers of race and class, underlies many instances of noncompliance and dissatisfaction with care.

In recent years clinicians and social scientists interested in these problems have used the heuristic device of distinguishing between *disease* and *illness*. Physicians diagnose and treat disease, the "malfunctioning or maladaptation of biologic and psychophysiologic processes in the individual," whereas patients experience illness, "personal, interpersonal and cultural reactions to disease and discomfort."[3] Problems associated with disease are routinely noted on a patient's chart; those associated with illness, however, may or may not be recognized by a physician and, if so, may or may not be dealt with or made a part of the medical record.[4-6] It has been suggested that the routine

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eliciting of a patient's explanatory model of illness uncovers areas of potential conflict and allows negotiation of treatment to occur.

My purpose here is to describe some traditional beliefs about health and illness widespread among members of the black lower class, to indicate how these reflect their life experiences in a culturally appropriate manner and to show that such beliefs are clinically relevant and should be discussed in a medical encounter.*

World View and Health Beliefs

OK, now, when I taken sick, when this lady did this to me, it was Sunday. Tuesday, I had this big old green plant, it was in my living room. When I went to bed that night I looked at my plant, I put the light out and I went upstairs to bed. The plant was green and pretty, big old plant. And that mornin' I came downstairs and it was brown, it had *cooked,* just that brown, overnight. They say if you got a green plant in your house the power will burn the plant up, but if you keep aputtin' plants in, green plants, it cannot get to you until it burn the plant up. Then it's really controllin' *you,* then. Can't no plant live in your house under that. Keep aburnin' the plants, [it'll] keep away from you.

MRS MARYA W, 1983
Personal Communication

At the time Mrs W got sick she had not heard that green plants can keep "the power" from humans and, so she believes, the fact that her only plant died allowed the power "sent" by an enemy to attack her. It would be difficult to imagine a more graphic example of a fearful view of the world—not only is there *power* about, but it can be harnessed and directed and sent into one's home to do harm. Her illness, she felt, was not "natural."

The way that many poor black persons experience their world is reflected in their use of the terms "natural" and "unnatural." All events, including illness, may be classified along these lines. It is a perception of reality inextricably bound up with religious belief, so that natural versus unnatural are closely allied with good versus evil or godly versus ungodly. Natural events take place in the world as God made it and as He intended it to be. In health terms one must take care of not only the body but the soul. "Natural" illnesses in this system may be caused either by failure to take care of the body or by sinful behavior. Such ideas are not foreign to physicians, though "sin" may not appear as an objective cue in the problem-oriented medical record.

"Unnatural" events, in contrast, are outside the world of nature and do not follow natural laws; by extension they are sometimes seen as the work of the Devil. They are frightening because by definition they are not amenable to the rules governing everyday life. They are based on the belief that there are persons with extraordinary powers to change the course of natural events, powers that they may use for their own ends or hire out: if the result of their machinations is an illness, it is an illness no physician can cure. These ideas may be foreign indeed to physicians, who may view patients with such beliefs as deserving of a psychiatric consultation. They are more readily understood if viewed as a metaphor for a deep and abiding mistrust of others, of a belief that, given the chance, everyone will seek their own advantage.

Sociologic and anthropologic studies of the black lower class reveal just such a belief: that the world is a dangerous and unpredictable place where attack may come at any time from a variety of sources and where the only reasonable position is to be on guard. Poverty, racism and chronic unemployment have created an environment wherein a child learns early that adults cannot always be depended on as their resources are so slight that it is necessary to "go for yourself" to survive and to manipulate others so as not to be manipulated by them. The result is a hustle-or-be-hustled world where friendships are fragile, male-female relationships brittle and even relatives not always to be trusted as they, too, must do what they can to get by.[1,10-16] In such an environment it is not surprising that many see the world as a hostile place where "exposure" leaves the body vulnerable to cold and damp, where God may "strike you down" for sinning and where an envious neighbor may "put something on you" by using evil magic. And it is not surprising that out-of-the-ordinary means are used for self-protection; attempts to control the environment by magic and religion are common where ordinary means are absent or unavailing.[7,17-19]

Maintaining Health and Preventing Illness

I feel like it's the care that they take of theirselves. That's what I think, I don't know. I feel like they exposes theirselves too much, and don't take enough care of theirself like they should. That's one reason that I can get around and do things now at my age! Now I've worked hard all my life, ever since I started at ten years old. But otherwise I've taken care of myself. And I never was the goin' kind! I didn't work all day, and then goin' half of the night and all like that . . . .[15(pp31-32)]

Mrs P, aged 82, also credited her long life and good health to the fact that she had always relied on her own herbal remedies, "my system ain't never been poisoned up by no medical doctor." The belief is that if people would use "mother wit" they could stay healthy almost indefinitely. The key word in staying well is moderation: a moderate and healthy life-style includes proper diet, rest and exercise. The body, if protected from extremes of heat and cold, adequately fed, kept clean inside and out, kept limber by work and exercise and properly rested, should remain free of most health problems. There is a special emphasis on monitoring the state of the blood, thought to mirror the state of the system, and on the processes of digestion and elimination.

Those at the extremes of age are recognized to be more susceptible to health problems and to require

*Information to be presented has been drawn from research by anthropologists, sociologists and folklorists on the black lower class; the medical literature; material from the folklore archives at the University of California at Berkeley and the Center for the Study of Comparative Folklore, UCLA, and ethnographic studies of black medical beliefs and practices. Special note should be made of the University of Miami's Health Ecology Project, a five-year study of the health beliefs and practices of 100 families from each of the five largest ethnic groups in Miami's inner city—southern blacks, Puerto Ricans, Cubans, Bahamians and Haitians.[7-9]

special protection. Women, too, are felt to be constitutionally weak. They are especially prone to illness when experiencing vaginal blood loss, as the body is seen as "open" and weak at that time.

It is not enough to simply take care of the body, however; ideas about health maintenance clearly show the belief that the body, the soul and one's personal relationships must *all* be properly tended. Every adult is responsible for knowing how the body functions, when it is especially vulnerable and how it must be cared for; every adult is responsible for keeping his or her relationship with God in order, and every adult is responsible for not acting in a manner likely to engender angry or envious feelings in others. "Act right!" is as important as "Eat right!" in most traditional medical systems.[2,18,20-23] There is little sympathy for a person who flagrantly breaks the rules, bodily, spiritually or socially: if one then gets sick, well, "you done done it to yourself!"[18]

Preventive measures also combine the practical, the magical and the religious: keeping the body clean, well-fed and warm will keep away certain illnesses—but so might wearing a string with nine knots around the appropriate part of the body, reciting a certain psalm, carrying a High John the Conquerer root in the pocket or burning a properly colored candle. Any city with a large black population has a candle shop where a variety of products are sold to help customers get what they want or need—candles, oils, incense, amulets and charms, aerosol sprays, powders, religious artifacts—all are available, along with booklets on their use to attract health, love, money or protection.[7,24-28]

Human nature being what it is, care is *not* always taken, of course—people stay out all night, drink too much, eat the wrong foods, fight with their neighbors, fail to say their prayers, forget to wear their protective charms—and illness occurs. Resultant symptoms may (from the view of orthodox medicine) wander confusingly from one area of causation to another. A stroke, for example, may be blamed on stress, impeded menstrual blood, eating the wrong foods or witchcraft. Folk diagnosis has as much to do with assessing in which areas of a victim's life care has not been taken as with the nature of the symptoms. A problem initially seen as natural may come to be seen as the result of evil magic if it fails to respond to appropriate treatment within a reasonable time.

Illness, whatever the cause, is viewed almost literally as an attack: all at once cold "enters" the body, God "strikes down" a sinner, the power creeps into a house, "put on" a victim by an enemy. Once the attack has taken place, the illness is spoken of as if it were a tangible presence in the body, something that x-ray films can "see." In some instances it can lurk undetected in a body for years, manifesting itself only as a person begins to weaken with advancing age. The cure may be instantaneous, so that the problem is described as "driven out" of or "taken off" the body. The idea of chronicity is therefore poorly developed and, in fact, most health problems are seen as curable if the proper remedy, the right physician or a more powerful healer can be found—if not, God can cure anything should He so desire.

Natural Illnesses

Well, in other words . . . it's *exposure,* that you get sometime when you're young in your body. Through your system as you get older, it take effect . . . dampness and not takin' proper care of yourself. Goin' out in bad weather and rainy weather, you expose yourself. Pores are open. You're subject to takin' a complaint, in through the blood . . . kind of grows into the system, and as you get older, it works with you.[18(p41)]

One of the first and most frequent answers to the question, Why do people get sick? has to do with the entrance of cold into the body. Other popular explanations are dirt, in and out of the body, and an injudicious diet. The impact of all of these may be assessed by examining their presumed effect on the blood. There is an extremely elaborate system of beliefs about the nature of blood and its functions, beliefs responsible for a wide range of self-treatment practices. Blood is seen to vary across a number of dimensions and is always in flux, responding to external and internal stimuli. Blood is spoken of as good or bad, clean or dirty, thick or thin, high or low and sweet or bitter. The extremes are dangerous and in a healthy body blood is not too high or too low, too thick or too thin and so forth. Many of the beliefs about blood to be described are found among white southerners as well, and there are strong parallels in the beliefs of immigrants to the United States from Haiti, Jamaica, the Bahamas and the Cape Verdean Islands.[8,20-22,29,30]

Cold as a Cause of Illness

Blood is believed to vary in its degree of thickness or thinness according to ambient temperature and relative age. The very young and the very old are believed to have thinner blood and thus are more vulnerable to illness. Normal blood should automatically thicken in winter to protect a person against acute and chronic problems associated with cold. It "thins down," sometimes with the aid of home remedies, as spring approaches, to ready the body for hot weather. Acute illnesses caused by cold include upper respiratory tract infections associated with increased mucus production, colds, flu, bronchitis, pneumonia and the like, and a disorder known as "quick TB," greatly feared by southern black and white women.[31] Lillian A's physician said that she had chronic cardiac disease, but she was never quite convinced. She believed that her shortness of breath was caused by breathing in cold or damp air, which made her "wheeze":

Now, just like this cough I have, now I don't really feel that it's a cold. And yet I *know* it's *cold* in there, because the main reason of the coughing, I get that little lump of phlegm or mucus in my throat, and I have to cough until I can get it out. And of course I know that's cold in there.[18]

She died of congestive heart failure not long after these remarks were made.

In later life, cold is blamed for the development of arthritis. The exposure in this instance may have taken place early in life without symptoms, but it is believed

that the cold and damp that have entered the body may "settle" in the joints. Such "old cold" will wait until a person is old and weak and has thinner blood, and then it will act:

Oh yeah, I have arthritis. Here they call it arthritis, but it ain't nothin' but rheumatism. See, I worked so long, I worked a long time, and the cold settled in my joints. Standin' in the cold catchin' the buses and things. And you know how much cold you accumulate.[18(p42)]

Cold is seen as especially dangerous to women in the childbearing years. The uterus is believed to be "open" when vaginal bleeding is occurring, and menstruation and postpartum and postabortion bleeding are alike dangerous. Cold is believed to enter the body, already weakened by blood loss, at that time. The result is much like stopping up a sink: blood, clotted by the cold, backs up into the body, causing headache, stroke, elevated blood pressure or the oral hemorrhages of "quick TB." The fear of such eventualities underlies a common proscription against getting chilled, bathing, shampooing the hair, walking in the rain and so on, when vaginal bleeding is occurring.[32,33]

No, I don't think you should bathe. When I was growin' up my girlfriend she died from bathin' during her menstruating period. They say it stops you, stops your womb up or somethin' up there, the water does. She was taking a bath during her menstruating period and she died in the tub. Another reason I don't think you should be in too much water is you'll catch cold. You'll catch cold because your veins are open.[17(p91)]

This woman's 18-year-old daughter reported that when she went into labor her mother insisted that she bathe and shampoo her hair, as she would not be able to do either again until after the cessation of postpartum bleeding. The exposure associated with cold-related problems is relatively easy to avoid: wear protective clothing when the temperature is low and avoid cold air *and* water if bleeding vaginally.

Dirt as a Cause of Illness

If the system's not clean, throws you into a deep sickness. Everybody's blood's not clean . . . When spring comes, birds start mating. Fishes in the water start mating. The sap is rising and impurities start rising too. If your system's defiled, why you're liable to come up with *anything!*[18(pp38–39)]

A dirty body is a sick body. Blood is the vehicle through which "impurities" (vaguely associated with "germs") circulate through the system. A body becomes "defiled" by failure to bathe, impeded menses, irregular bowel movements and sexual excess. The belief that a body must be "cleaned out" to stay healthy is by no means confined to ethnic medical systems, of course, as the most cursory viewing of television advertising shows. According to one national survey, two thirds of the adult population of the United States believe that a daily bowel movement is necessary for good health.[34]

Just as mucus in a body is associated with cold, impurities are associated with heat—fever, inflammation and skin eruptions. The latter, ranging from measles to syphilitic chancre to skin cancer, represents "something in the body trying to come out." It is thought dangerous to interfere with any sort of natural process or with any attempt of a body to heal itself. Cold is believed to suppress a rash, causing it to "go in" on the body with devastating results.

The most common result of the concern with dirt, however, is a preoccupation with the gastrointestinal tract and constant monitoring of what goes in and what comes out. There is a dependence—sometimes an overdependence—on laxatives, which begins at birth. "I don't worry about my grandbaby being constipated. I puts a spoonful of that children's laxative in her bottle every night!" (personal communication, Odelia K, 1982). Many women also believe that "the little red hives" need to "come out" on a new infant to rid its system of the accumulated filth of the intrauterine environment, thought filthy because the mother did not menstruate during pregnancy. If hives do not appear a child may sicken and die, and catnip tea is often given to hasten the eruption.[17,31,35] One infant brought into a Michigan pediatrics clinic was admitted to hospital for weight loss at 3 weeks of age. One reason for his failure to thrive was poor caloric intake due to the several bottles of catnip tea he was being given every day. He had not yet broken out in the little red hives, his mother said, and she was concerned about his health (Nancy Spates, MD, Resident in Pediatrics, Graduate Medical Education, Inc, Lansing, Mich, personal communication).

It is widely believed that the main purpose of menstruation is to rid the body of dirty and excess blood, and any interference with normal menstrual pattern is frightening. Diminished flow is of concern, "I guess I get nervous because I wonder where the flow is going. It might back up," said one woman in the Miami study. "Where is the bad blood going to be stored?" asked another.[36] Increased menstrual flow is just as much a problem because that can weaken the body. For these reasons many black women have very negative views of contraceptive methods that in any way change menstrual patterns.[32,33,37] It is "not natural" to interfere with the body's attempts to clean itself.

As mentioned, there is a belief that the uterus is open during the menses to allow all the tainted blood to escape. It follows that many women believe that they are "safe" for unprotected intercourse at midcycle, when the uterus is "closed." Such ideas, combined with a very powerful cultural prohibition against intercourse during menstruation (81% of all black women in a Detroit prenatal clinic sample and 91% of the teenagers in the sample subscribe to this taboo) are bound to contribute to unwanted pregnancies.[37]

Folk ideas about venereal disease are also associated with dirt in the body, often referred to as "bad blood." In studies conducted in prenatal clinics in two Michigan cities, many black women, though generally aware of the role of sexual contact in contracting venereal disease, also believed it can be caused simply by being dirty: failing to bathe after a menstrual period, wearing dirty underclothing, living in dirty surroundings or having sex with too many partners, none necessarily

infected. Many also believed that the Pap smear is a test for venereal disease, and some had been insulted at the suggestion that they have one done.[32,37,38] The Miami study revealed similar misunderstandings between black women and their physicians on the causes and proper treatment of salpingitis—"pus tubes" in the folk system—believed by the women to be the result of dirty or "poisoned" blood.[9]

Prevention of health problems caused by dirt has to do with keeping the body clean (and cleaned out) by bathing, the constant use of laxatives, avoiding behaviors that might stop up vaginal bleeding and sexual moderation. In the springtime there may be an additional "cleanup": additional laxatives may be taken, as well as sulfur and molasses (thought to open the pores so that impurities can escape), and poke greens eaten to purify the blood. Here, too, moderation must be practiced: "You can't take a blood tonic all the time; it would work in the blood too forcible, strip things out that you didn't want out."[18] One woman carefully hides "liver" pills in her husband's oatmeal each spring; he just as carefully fishes them out when she is not looking.

Improper Diet as a Cause of Illness

I used to have the high blood pressure but the doctor says I don't have it no more, so I quit taking the pills. They made me sick anyway. Now when I feels woozy I just takes me a pinch of epsom salts.

SADIE W, 1982
Personal Communication

"High blood." The diet is instrumental in causing two conditions that have a good deal of clinical significance, "high blood" and "low blood." The terms high and low may refer to either the amount of blood in the body or a shift in its location—that is, "high blood" may be too *much* blood or it may be that a normal amount of blood is present in the body but has suddenly shot up into the head. Changes in blood volume and shifts in location can result from improper dietary practices or emotional shock or both. High and low blood are acute conditions with recognizable symptoms. They are usually treated with short-term regimens of dietary manipulation and home remedies. Unfortunately, they are often terminologically confused with high and low blood *pressure*.[8,9,17-20,22,39,40] Arizona women defined high blood pressure as "too *much* blood, the blood goin' to your heart, to your brain or somethin'," and as "an overflowin' of blood, a clogging, from eatin' too much and gettin' too fat, the blood goes up to your head too fast." As usual it is a person's own fault: "But you know you can help that yourself, just don't eat all that rich food."[18]

The sorts of foods that are believed to cause these changes in the blood may be described simply as "too rich," or they are those red in color—beets, carrots, grape juice, red wine and red meat, especially pork.[2,8,17,18,41] These are usually referred to as "blood builders." In parts of the South they are said to make the blood too "sweet," as well as cause a rise in "pressure," however that is defined.[20,40]

Symptoms of high blood (pressure) include headache, dizziness, spots before the eyes and "falling out," a term used for sudden collapse. Such symptoms indicate that an abnormal amount of blood has reached the head and, if not "brought down," it may lead to stroke or death. In Miami, Bahamians refer to "falling out" episodes as "blacking out," and Haitians as "indisposition." Weidman believes that "falling out" is a true culture-bound syndrome, a seizure-like disorder often diagnosed as epilepsy in health care settings. From an outsider's view, "falling out" may be psychogenic in origin; to an insider, it results from a state of the blood or, if this does not respond to treatment, to a hex.[19]

Treatments for high blood include foods, herbal teas and other remedies that have the properties of "thinning" the blood, "cutting" it or "bringing it down" to where it should be. Some of these serve to open the pores to let the excess be sweated out; others open the bowels to eliminate it in that fashion. Menstruation helps to get rid of excess blood for women and, if flow is diminished, it is thought that a rise in blood pressure might result.[36]

Just as red items symbolically "build" blood, many of the treatments to "lower" blood are white or colorless. In the South many herbal remedies are used to treat high blood, sometimes referred to as "bitters," as they neutralize the "too sweet" condition of blood associated with the problem. Such exotica as bullfrog urine mixed with bits of garlic and onion have also been reported as antihypertensive.[20,22,30,39,40,42] In urban areas where wild plants are not available (not to mention the dearth of bullfrogs) treatments are more likely to be astringent items such as vinegar, lemon juice, olive or pickle juice, garlic, epsom salts and the like.

The following anecdote shows a misunderstanding that arose when a physician made a diagnosis of high blood pressure, which the 64-year-old black patient mistook as "high blood" pressure: Arnella L woke up one morning unable to see and unable to use her right arm; an ambulance was called and she was taken to a hospital that provides health care to indigent persons. There she was examined by "one of them student doctors" who said that she had had a "light stroke." The hospital was full so she was sent home in the care of relatives. First, however, she was provided with a bottle of pills that she was told she would always have to take. "Now that don't make no sense," was her response to that directive (although she did not express this belief to the physician) and the medicine was discarded the same evening without a single dose being taken. Instead, she embarked on a series of treatments that she—and her neighbors—thought more appropriate to her problem, blood that had "boiled up in the brains" from eating too much rich food. She slept sitting up for several nights, the better to allow the blood to drain back down into her body. She began a nine-day regimen of drinking a solution of honey and vinegar in hot water. The minister of her church came to pray for her to complete the cure. She reported that she "felt the stroke leave" her body when he placed

his hand on her forehead. She also instituted preventive measures on the advice of an elderly aunt:

The 15th of February I was right at death's door. My blood pressure was run up so I couldn't see nothin', couldn't do nothin' but feel my way. My auntie said, 'Well, honey, your sight will come back, it will eventually come back. But you drink you a teaspoon of vinegar in some water and that will prevent another stroke. And keep your hand rubbed in it, in white vinegar. Take a teaspoonful of that vinegar in water, that'll thin your blood, too, that'll prevent your havin' another stroke.'[18(p35)]

Commented her niece bitterly, "The doctors didn't do nothin' for her, that's for sure." It is not surprising that southern blacks are reported overrepresented for noncompliance with diet and medication for hypertension in the ambulatory clinics of Miami's Jackson Memorial Hospital.[9]

"Low blood."

Darlin', low-blood pressure is not enough blood to go through. They have to give you iron, they give you iron pills, iron tonic to build the blood. Then they give you food to eat, tell you to eat beets or liver; some of 'em, they'll tell you to drink wine, red wine.[18(p36)]

"Low blood" is conceptually allied with anemia but may be terminologically confused with low blood pressure. It is "sort of like when you're anemic, your blood is low from not eating the right food."[41] The wrong sorts of foods are too many pickles or olives, too much vinegar, lemon juice and garlic and not enough red meat. It may also be caused by taking "high blood" remedies too long. It was this belief that caused Arnella to throw away her antihypertensive pills; to her it would be folly to take such medicine for life.

The symptoms of "low blood" pressure are weakness, lassitude, fatigue and, again, "falling out." Treatments are the ingestion of red foods and beverages seen as blood building, as listed above. These in turn must not be taken for too long, lest the low blood be again transformed into high blood.

In a public clinic in Michigan a 62-year-old man came in for follow-up care for hypertension, which had been under good control with a diuretic for over a year. At this visit his blood pressure was significantly elevated; on questioning he said that he had not taken his medication since his last visit a month earlier. A review of his records showed that a routine complete blood count was done at the previous visit, and the leukocyte count had been low. A physician told him that his "blood count" was down and that it would be checked again at the next visit. The patient interpreted that as "low blood" and believed that his faithful taking of the diuretic had *indeed* "brought down" his blood, damaging his health in the process. The physician had not heard of the entity "low blood" and the patient did not know that low blood, low blood pressure and low blood count were not all equivalent terms. A discussion (with pictures) of the difference between the cellular components of the blood and blood pressure ensued, and the patient promised to begin taking his medicine again.

Improper Behavior as a Cause of Illness

So many time the Lord get vexed with us when we do things. Like sickness, I would say sometimes is a whup to us, just like whuppin' a child. So many times we have to be taught a lesson, a sickness sometime bring us down to make us serve the Lord's will. Sometime we don't know to say 'Thank the Lord,' and we don't know how to praise the Lord and thank Him for things He did for us. You can invite it in yourself. If you live a real good life for God, it's just like children: if you got good children, you don't have to punish 'em. Sickness and different things comes like a whuppin', a reminder. The Lord would heal all the peoples if they would ask the Lord to heal 'em. But the people, they forget God.[18(pp53-54)]

It has been estimated that more than 90% of poor black people are church affiliated and religion is a very important component of ideas about health and illness. Remarks about everything from causes of health problems to the best ways to cure them are often reinforced with "It's in the Bible" or "The Bible tells you that." The relationship with God (a stern but loving parent) is seen as a very personal one, and He is thought to keep close watch on the behavior of all.

It is believed that God can and does punish transgression with illness.[2,20,22,23] The assessment of a given health problem as divine punishment is probably based on feelings as to whether or not a person (or a family) *deserves* such an occurrence, not on any particular constellation of symptoms. However, the problem is usually sudden and dramatic or something visible, incurable and long-lasting (or both), giving a sinner time to contemplate his or her misdeeds. Such illnesses have been called *personalistic,* in that a victim is not randomly attacked but has been selected by some sentient outside force for reasons known and understood by the social group.[43] Belief in such punishment is probably found among all social classes and ethnic groups, though ideas about what sorts of behavior merit such action differ. Greed, failure to share and lack of charity rank high on the list of punishable behaviors among the black lower class—a powerful means of social control.

Infants and children are often the innocent victims of their parents' misdeeds and parental sin is commonly blamed for deformity, seizure disorders or retardation. If the external world is seen as threatening to an adult, the intrauterine environment is certainly no haven for a fetus, trapped and helpless, dependent on the mother-to-be's behavior during her pregnancy. The idea that an unborn child can be "marked" by its mother's actions is still widely believed, and the belief that God will so mark an infant if the mother misbehaves serves to curb undesirable acts.[21,33,38] If a pregnant woman sees a crippled person and laughs, for example, God may "put the same thing" on her infant to remind her to be more charitable in future. The sight of the crippled child is a constant reminder to her (and everyone else in the neighborhood) as long as she lives.

As God punishes He also heals, and religious belief can be a powerful aid for recovering from illness. A dramatic example is the case of a 68-year-old black woman whose postoperative course from partial colec-

tomy for resection of carcinoma required no pain medication whatsoever. She reported that she had minimal discomfort because a bright band of angels stood around her bed, protecting her.[44] A patient's minister can also be a useful ally if problems of a religious nature arise in a clinical situation.[45] In those instances wherein persons feel that their problems result from their sinful behavior, irrespective of the orthodox explanation for the problem, it should be recognized that a patient may have social and religious fences to mend as well as a medical regimen to follow.

Unnatural Illnesses

I was in church one day and I had the headache and I didn't have my medication with me. So I asked the usher to get me some aspirin from somebody, so she got 'em from this lady, I won't call her name. And when she give me the aspirin the headache went away but I took sick to the stomach. And I just kept on gettin' sick to the stomach, sick to the stomach. Then I just got where I couldn't *do* nothin' for myself, and I got to where I just got down in bed, couldn't get up. And I got so sick I just got almost too weak to talk, and I couldn't eat, I couldn't stand the smell of food. 'Til one time I had a vision like, that this lady came to me with two pills in a pan, that was in the vision I had, she was shakin' these two pills in this pan. Said, 'if you don't take 'em, these pills, you're gonna die!' And I told my husband then, I said, 'This lady came to me with these two pills, I remember, that's what I taken in church, two aspirin from this same lady,' and I said, 'seem like sumpin' is wrong and I don't know what it is.' So my sister-in-law told me that he'd better take me somewhere, that I probably *would* die! Well, *she* knew who to go to, cause this same lady had did sumpin' [to her], causin' her to have bats comin' into her house, this lady had did that to her. And when I told her about this vision I had, she say, 'Yes, that lady is doin' sumpin' to her, so you better get her to somebody.'

MRS MARYA W, 1983
Personal Communication

Marya believes that a woman "poisoned" her because she wanted her husband. From an outsider's view, her symptoms might have resulted from acute situational stresses because at the time she took to her bed everything in her life seemed to have gone wrong. In a period of a few months she had been injured at work and laid off; she was unable to keep up her mortgage payments and was evicted from her home; her parents were divorced and her alcoholic father moved in with the family; her second husband discovered that he was not divorced from his first wife, refused to legalize the situation and became impotent; her oldest son sustained permanent brain damage from the use of angel dust, and her oldest daughter, 16, announced that she was pregnant and was going to quit school. Small wonder that she had headaches. Small wonder that she believed "the power" had entered her home, frying houseplants and generally causing mayhem. She had been brought up to believe that those who wish you ill can "do something to you" by magical means and that those persons are numerous. The personification of impersonal forces enabled her to identify her problems as "hoodoo" and to take action, however foolish that action might seem to a middle-class observer.

The use of magic for manipulating life events is common where the environment is seen as hostile and dangerous and ungiving, and where people have little control over what happens in their lives.[19,26,46-48] "Unnatural" illnesses are terribly frightening because they are outside nature; ordinary people, including physicians, *especially* physicians, are unable to deal with them effectively. It is commonly said, in fact, that one symptom of an unnatural illness is that "the more you go to the doctor the sicker you get." One explanation is that going to a doctor "aggravates" the power causing the illness.[49] Charms and spells are used to control the behavior of others: to win love, keep a spouse from straying, take someone's lover from them or avenge a slight from a neighbor. Problems of love and envy are the reasons given for most of the reports of hexing behavior, and the abnormal "control" of a victim causes physical or behavioral changes (or both). Reports of persons who believe that witchcraft is at the root of their health problems have appeared in the clinical literature in the past few years.[50-58]

Reported symptoms of magical illness range from pseudocyesis to headache, but most can be divided into two broad categories, gastrointestinal and behavioral. In most instances it is believed that the fix or hex is administered in a victim's food or drink, and it is often referred to as "poison." Snakes, frogs or lizards may be introduced into the body in the form of eggs or powder, which hatch or reconstitute themselves and take up their abode in a victim's blood, stomach or head. The thought of eating or drinking something evil that can then literally exist in the body must be psychologically devastating. Many blacks who believe in witchcraft are very careful about where and with whom they eat, and in extreme cases may eat no one's cooking but their own. Loss of appetite, nausea and vomiting, food that does not taste right, diarrhea or "falling off" (weight loss, especially unexplained weight loss) —any sort of gastrointestinal problem that does not quickly respond to treatment—may be interpreted as unnatural, especially if there is conflict in a victim's personal relationships. Marya W's life was already troubled when she accepted two aspirin from a lady at church, and her benefactor had already shown ill will toward members of Marya's family and willingness (so it was perceived) to use evil means to express it.

Any sort of behavior that is out of the ordinary, ranging from inability to carry out usual tasks to outright mania, is also frequently interpreted as the result of magic. The belief that animals can be introduced into and survive in the body has a behavioral parallel in the fear that a victim of magic can be made to behave like an animal. One woman reported that a man she knew had been bewitched and had "howled like a dog 'til he died"; someone who hates a pregnant woman may curse her so that her infant will bark like a dog.[18,33] A number of observers have noted that mentally ill black patients frequently believe they are the victims of hex.[25,49,52,54,59,60] Nearly half of the patients interviewed at one mental health facility "attributed their own illnesses to the effects of malign

magic perpetrated by a close relative or friend who often figured prominently in the presenting symptomatology of acutely psychotic patients."[61] The problem is to differentiate between those patients whose symptoms have been caused by *fear* of a hex[55] and those whose symptomatology of mental illness is taking a culturally appropriate form.

Almost any health problem may come to be seen as "unnatural" if it does not respond to ordinary treatment, or if a physician does not seem to know the cause of a problem. A physician does not have the power to remove the results of a spell, as the spell was put on by someone with out-of-the-ordinary abilities. Only a healer with "the power" can take off an unnatural symptom, remove poison from the body, drive the magical snake from a vein. Unfortunately, a person with the power to take off may also, for a price or on a whim, be both willing and able to put things on as well.[8,19,27,59]

Traditional Healers

Unnatural sickness, doctors can't do nothin' *for* it, y'know. OK, for instance I know *this* story, that my *grandmother* was rooted by a woman over her own husband, my grandmother's husband. And this lady had did sumpin' to her so she had a *sore* on her leg, you see, and this sore didn't never *heal!* And she went to the doctor, she went different places, and they couldn't do *nothin'* for her! It was a open sore, open through the wall, so she decided to go to a root man and this man told her that somebody had put a *root* on her . . . and he gave my grandmother some kind of special *salve*. What it was I don't know, he gave her sumpin' to *rub* on it, keep puttin' on it, bathin' in it. And she did it. And sho 'nuff, right before everybody's eyes a snake crawled out of it. And they say it was a snake, whether it was a baby snake, big snake, I don't know. I remember this story when I was little, and I couldn't forget it, couldn't get it out of my mind every time somebody mention roots to me. She said it *crawl* outa her sore, crawled outa that opening that was in her *leg,* crawl right clean outa there. And they killed it. They was hittin' at it and it just disappear, just like black magic, like Voodoo or whatever.

GERALDINE B, 1983
Personal Communication

There is no lack of alternative healing sources for a black patient who is alienated from the orthodox medical system, or whose problem will not or cannot respond to orthodox care. There is a great variety of traditional healers available and they may be used serially, in tandem with or instead of biomedical professionals. Their treatments may be public or private, religious or secular, reasonably priced or outrageously expensive. Some may use "the power" (and their clients' fear of that power) to manipulate and extort.* They include out-and-out charlatans and talented therapists. We have very little information about their practices; they tend to be wary because of licensing laws. It is probable that successful healers share the world view of their clients (or understand it well enough to use it in counseling and advising), make diagnoses that seem appropriate to that world view and use treatments that both practically and symbolically put a patient back into balance physically, socially and spiritually. Returning to the disease-illness dichotomy, such healers "may or may not provide effective treatments for any particular disease; their chief contribution is their recognition and management of the life problems that illness poses, including personal, marital, family, work, financial and related difficulties that frequently accompany sickness."[2]

When Marya W traveled 50 miles to see the Reverend X, who had successfully removed the bats from her hexed sister-in-law's house, he took a history of recent events in her life and agreed that the problem was caused by the aspirin given to her in church. These, he said, had "thinned out" the lining of her stomach until it was like tissue paper; if she had not come when she did, she would soon have died. His treatment seems both common sense and psychologically apt: he (1) gave her a "prescription" to take for seven days that consisted of a mixture of white wine, white milk and the white of egg to "build up" the stomach lining; (2) gave her incense and candles to burn to drive the evil from her home; (3) gave her salts for a series of ritual "cleansing" baths, to remove the last vestiges of evil from her body; (4) told her to sleep with a Bible under the mattress, opened to the 23rd Psalm, and (5) strongly suggested that she find another church to attend. At the end of her seven-day treatment she was cured of her symptoms, though she believes that the poison somehow eroded the lining of her stomach so that she will be more vulnerable to stomach cancer in the future.

Conclusions

There is a viable system of traditional beliefs among many lower class black Americans that can affect every aspect of their interactions with the professional system of medicine. It is a model of health and illness that, although there may be overlapping vocabulary, is often strikingly different from the model of orthodox biomedicine. Failure to elicit a patient's understanding of an illness, its cause and how he or she believes it is properly treated can result in anger, frustration and noncompliance. Failure of physicians to include questions about the life-style of patients, presence or absence of a viable support system or their concerns about the effects of illness on daily life may send them to a traditional healer who *does* understand that such matters are important. Listening to a patient's view of health problems in an interested and sympathetic manner will elicit areas of possible conflict but also beliefs that may be strengthened and reinforced. The belief that a moderate life-style promotes good health and long life and that persons must actively maintain their own health can be used to advantage in health education programs. Others, of course, have much more potential for engendering practices seen as dangerous from the vantage point of biomedicine, as when the notion of "high blood" leads to misunderstanding of a condition like hypertension, with its high prevalence among black Americans. Even here, however, both patient and practitioner are interested in the body and how it functions, and the discovery of differential ex-

*References 1, 8, 19, 20, 25-27, 42, 49, 56, 57, 59, 62-67.

planations provides the basis for discussion and negotiation of treatment.

The category of unnatural illnesses cannot be dealt with so easily, however; because it does not exist in the scientific model of disease, there is little or no basis for negotiation. Educational problems will not eliminate a belief in hexing, reflecting as it does an attempt to control life experiences by those who, in fact, have control over nothing. Such negative life experiences are *not* going to disappear in the near future: the Center for the Study of Social Policy reports that in measures of income, poverty and unemployment, disparities between black and white Americans have not lessened since 1960, and in some instances have worsened (Slade M, Biddle W: "For many blacks the gap remains," *The New York Times,* July 24, 1983, sect E, p 22). "The ultimate cause of the curse lies in economic, racial and political inequality, not in the hands of the sorcerer. It lies in unemployment, poverty and negative self-image, not in a bag of roots and graveyard dirt. It rests in a social environment so hostile that the individual would be a fool not to believe in the evil intentions of others. The real cure lies not in medications or mojos, then, but in a restructuring of American society which would truly result in equality for all."[59]

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Japanese Responses to Social Change—Making the Strange Familiar

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Understanding the concept of a "sense of coherence" can be useful in trying to account for successful and healthy adaptations to situations of social change and migration. Certain fundamental dynamics of social life in Japan contribute to a sense of coherence in the lives of Japanese today. Analysts of modern Japan have noted that it has not become a replica of western societies in that primary social groups take precedence over individual needs and autonomy. Moreover, although the Japanese personality may be characterized as multilayered, one dominant aspect is the tendency to suppress negative feelings —towards intimates, family and those in authority. This tendency has implications for the patient-physician relationship, which tends to be ritualized to protect a patient's innermost feelings. Because there has never been a split between mind and body in Japanese thinking there is no concept of mental health that is separate from physical health; rather, patients and physicians readily accept that illness is an expression of stress on the social level. As a corollary, the responsibility for healing is felt to be in the hands of patients and their families, with physicians playing the part of skilled and sympathetic technicians.

Ascribing the origins of a cultural identity risks stereotyping, but understanding the reasons for the continuity of certain values in Japanese immigrants will enable physicians to use these values to advantage, and explains the healthy adaptation of these immigrants to the disruption of migration.

> *Western paper is to us no more than something to be used, but the texture of Chinese paper and Japanese paper gives us a certain feeling of warmth, of calm and repose. Even the same white could as well be one color for Western paper and another for our own. Western paper turns away the light, while ours seems to take it in, to envelop it gently, like the soft surface of a first snowfall. It makes no sound when it is crumpled or folded, it is quiet and pliant to the touch as the leaf of a tree.*
>
> JUNICHIRO TANIZAKI, 1934
> *In Praise of Shadows: A Prose Elegy*

For more than 15 years a group of social epidemiologists has been juggling numerous variables in an attempt to account for the variation in rates of coronary heart disease in men of Japanese ancestry. Their efforts have been highly influential in promoting some new lines of inquiry within their discipline. Marmot and Syme[1] found that a group of Japanese-Americans defined as traditional—that is, those who retained Japanese group relationships—had a coronary heart disease prevalence as low as that observed in Japan, while the most acculturated group had a prevalence rate that is comparable with that of white Americans. These differences cannot be accounted for by the risk factors such as blood pressure, serum cholesterol levels, smoking or diet that are usually considered of major importance in coronary heart disease.

The results of this work and other studies have led to increasing interest by epidemiologists in factors that protect from illness rather than in the causes of diseases per se. Hence, studies have focused on social networks and social support systems and several have produced convincing evidence of the value of familial and community ties as a protection against illness.[2-5] Antonov-

Refer to: Lock M: Japanese responses to social change—Making the strange familiar, *In* Cross-cultural medicine. West J Med 1983 Dec; 139:829-834.
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sky, in an innovative attempt to pull together the vast body of literature on stress, tension management, social supports and their relationship to health, postulates the need for a sense of coherence in one's life.[6] He defines a sense of coherence as a global orientation attributable to either individuals or groups and that "expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that one's internal and external environments are predictable and that there is a high probability that things will work out as well as can reasonably be expected."[6(p123)] This concept appears to have much in common with the idea of a "cultural ethos" or "world view" postulated by anthropologists many years ago[7,8] but Antonovsky's important contribution is to point out some suggestive links, many of which are already empirically established, between a state of health and a sense of coherence. He also reviews some of the cultural, social and psychological variables that contribute to a sense of coherence including early socialization, social supports and a stable environment but is quick to point out that there are "many sociocultural roads to a strong sense of coherence." Furthermore, he hypothesizes that a person with a good sense of coherence should be better able to successfully deal with a large number of life-change events including, presumably, migration and acculturation.

If one accepts a biopsychosocial approach to health and illness[9,10] and hence the view that a great number of diseases have psychosocial factors as their contributory causes, then it becomes incumbent upon a physician to try to explore those elements that facilitate a sense of coherence in a patient if the physician wishes to provide more than symptom relief. In the case of an immigrant, this approach becomes exceedingly complex because an immigrant is of necessity in a process of transition. Clinging to the values and behaviors of one's country of origin is unlikely to contribute to a response of "creative adaptation"[11] but, as the findings of social epidemiologists indicate, neither will plunging heedlessly into the melting pot contribute to a healthy adjustment.

Japanese immigrants are usually judged extremely successful in their adaptation to North America by the accepted forms of measurement: length of education, economic status and entry into professional occupations. The fact that the traditional Japanese value system incorporates an attitude towards work similar to that of the Protestant ethic[12] has frequently been cited as a major reason for the successful assimilation of Japanese immigrants[13]; several studies indicate, however, that the process is not always an easy one.[14,15]

'Soft Rule' and 'Ritualistic' Resistance: Japanese Concepts of Power and the Individual

Attempts to portray the origins of a sense of a cultural identity or a concept of self are, of course, fraught with the dangers of stereotyping. But it is apparent to both Japanese and western analysts that the process of modernization in Japan (if one looks beyond technology and popular culture) has not created a society that is a replica of a western prototype. In particular, the form that social interaction takes and the relationship of persons to the various groups to which they belong are very different from western examples. They are, however, of great importance in trying to understand both traditional and contemporary Japanese society and the people of which it is comprised.

A well-known Japanese intellectual historian, Kamishima Jirō, distinguishes Japanese sociopolitical development, which he describes as an "assimilating unitary society" from typical western development, that of an "alienizing composite society." He believes that much of western history is based on a pattern of conquest and subjugation of people that sets up situations of conflict and a questioning of political authority. Japan until World War II was a country that had never been overrun in historical times and whose culture had developed by absorbing and assimilating things from the outside by "making the strange familiar."[16(p8)] Georg Simmel[17] claims that for people to develop a clear conception of political authority and thereby to demystify it, they must have experience of more than one kind of authority; only thus can they learn that authority is not part of an inalienable natural order. Koschmann,[18] drawing on the work of Bellah,[19] Harootunian[20] and Kamishima[16] among many others, shows how the precept of authority is reflected in Japanese religious and ethical traditions and also reaffirmed through linguistic domains such as the distinction between *watakushi* ("I" or "me") and *ōyake* ("the public"). In the Meiji era (1868 through 1912), for example, "*ōyake* was always associated with high-sounding purpose: public tranquility and order, fairness, and the 'consultation of public opinion' *(kōgi); watakushi* was identified with irregular dealings, bad faith, selfishness, personal feelings and private desires . . . in the inevitable encounter between the realms, individuals were admonished, as a kind of moral imperative, 'to dissolve the personal and honor the public *(messhi hōkō)*'."[20]

The actual exercise of power in Japan has been characterized as "soft rule" in which the preservation of harmony and suppression of conflict takes priority over individual rights and needs; an employer's control over an employee, for example, is based on power and not on rights. Koschmann states "when oppression is soft and persuasive, feelings of dependency and relatedness persevere to obscure the irreducible atom of individuality and perpetuate the belief that what is real is to be found outside the individual, *between* himself and others rather than within."[18(p19)] Psychological studies reinforce this conclusion.[21,22]

In such a social system forms of resistance to the all-enveloping cloak of authority are not usually those of open conflict but tend to be less direct. Tsurumi,[23] a sociologist, using historical and contemporary sources, concludes that there are two types of resistance frequently used in Japan. She calls them "retreatism" and "ritualism." The tradition of voluntary or forced sepa-

ration from the community (retreatism) was called *yamairi* ("entering the mountains") and used to imply a permanent seclusion. In contemporary Japan there are estimated to be 90,000 people who have voluntarily undergone *ningen jōhatsu* ("human evaporation")[24]; they have apparently chosen "retreatism" as a form of protest, as have, perhaps, immigrants from Japan to North America.

The second form of resistance, ritualism, involves the preservation inside oneself of nonconformist values while outwardly conforming to established behavior patterns. Koschmann states, "Ritualism means the preservation internally of contradiction. It implies accommodation within the personality of mutually contradictory elements (including values, belief systems, emotional responses) rather than their external expression and resolution through conflict."[18(p20)] Japanese society as a whole can be best viewed as pluralistic or having multiple layers of value orientations and ideology,[12,25] and Tsurumi[26] characterizes both Japanese social structure and Japanese personality as multilayered; the psychological mechanisms of suppression and not repression appear to be dominant.

Ritualistic resistance is probably the most usual form of protest in Japan and, like retreatism, it does not lead directly to reform or social change. At times, of course, situations become intolerable and then protest becomes active and "expressive." The most notable recent examples of expressive protest are the ritual suicide of the author Yukio Mishima and the activities of student radicals in the 1960s. Rather than trying to implement social change through organized, instrumental action, such protest is designed to create "symbolic affirmation of [one's] own principles"[27(p111)] and also to try to provoke others to act by inducing guilt in one's antagonists.[21]

Somatization and the presentation of nonspecific complaints have been noted as frequent reasons for a visit to a physician's office in Japan[25,28] and though as a form of protest it may not be conscious, the research of both anthropologists and physicians indicates that the body is habitually used as a means for communicating stress and oppression.[29-31] Somatization can be interpreted as a plea for help and, like suicide, as an attempt to induce changes in the behavior of the people affecting one's life.

Social Relativism: The Self and Others

Every society appears to make some distinction between "ideal" and "actual" behavior but the Japanese language uses several dichotomies that indicate to what a fine art this discrimination can be developed. For example, one situation is distinguished from another according to whether it is defined as *uchi* ("in," "inside," "internal," "private," "us") or *soto* ("out," "outside," "external," "public," "them") and behavior is modified accordingly. But these distinctions are not fixed; they are rather fluid categories, socially relative and dependent, for example, on whether one is dealing with another person, one's family, a company or a foreign country.

A second dichotomy, that of *ura* (interior, or hidden from the public eye) and *omote* (exterior, or exposed to public attention), is also used to organize speech patterns and behavior vis-à-vis other people. Lebra distinguishes three usual combinations of the *ura/omote* and *uchi/soto* dichotomies that lead to what she characterizes as three familiar types of interactions in Japanese society—those of intimate, ritual and anomic behavior.[32]

Intimate behavior is guided by the concepts of *ura* and *uchi,* and though intimacy usually occurs between persons who are in frequent contact with each other, it can happen between strangers and is by no means limited to sexual relationships. Intimate behavior is spontaneous and confirms a sense of oneness, unity and solidarity. Intimacy is best expressed nonverbally; one is ultimately trying to attain *ittaikan* ("a feeling of oneness") in which one senses another's pleasure, pain and needs as acutely as though they were one's own.[32] Ordinary family life is not usually characterized, with the exception of a mother and infant, by intimate behavior except in moments of relaxation, such as eating, drinking or bathing together, when one is permitted to express one's innermost feelings. At times such as these the hierarchic and formalized relationships of daily life are stripped away to leave one "socially naked."

Ritual behavior is based on the notions of *omote* and *soto,* which are close to the concept of persona or mask. Much of daily behavior in the home, at school or at work is ritual behavior in which speech styles, gestures and postures are used that reinforce the nature of the social relationships between the persons involved. But, even in clearly hierarchic situations such as that of teacher and student, or doctor and patient, in moments of spontaneity and relaxation, ritual behavior can be replaced by intimate behavior.

The final form of behavior, anomic, is characterized by a combination of *ura* and *soto.* In situations of novelty or anonymity a person can act without restraint and in a "heartless" or "shameless" manner.[32(p131)] In real life, of course, these distinctions are not always consistently maintained but they are forms of behavior that every Japanese is socialized into[33,34] and that can be readily verbalized.

The Concept of Self

Doi, a leading Japanese psychiatrist, discusses the problem of totally losing one's sense of self by immersion in social relations and obligations.[22] Persons are normally expected to cultivate a personal identity or sense of self,[35] though success and achievement are measured in terms of the contribution towards one's family or other social group.[21] Inner desires and feelings are, naturally, frequently in conflict with the expectations of others, though conflicts such as those between "self" and "other," emotions and obligations and "private" and "public" are rarely verbalized.

I have dwelt at length on Japanese social relation-

ships because they represent the heart of what embodies a sense of coherence in Japan and many studies show the continued importance of these ideas.[36-38] Some observers believe, however, that they are not as pervasive as in previous times[39] and others stress the importance of not thinking of Japan as a homogeneous entity.[40] The implications of these concepts for the interpretation and management of illness will now be considered.

Responsibility for Health and Healing

Illness represents disorder, and the activities and explanations that people use to deal with illness represent an attempt to restore order and control. Medical activities and knowledge, both lay and professional, are shaped by their cultural context[25,30,41] and the core values that provide a sense of coherence to a person's life are also reproduced in attempts to interpret and attribute meaning to illness episodes. The same values are drawn on to structure relationships between physicians and patients, and patients and their families.

In Japan patients frequently state that they have put themselves completely into the hands of their physicians and during a physical examination they readily supply a large amount of information about their physical problems.[25,42] But Caudill and Doi also point out that the relationship between physician and patient has "a subtle quality of play-acting on the part of both participants which prevents it from being characterized as truly personal."[42(p381)] The situation is very similar to other close relationships in Japan, including familial ones, and is structured by "ritual" behavior. The body is objectified, and even though care and concern may be expressed, it is done so without a disclosure of innermost feelings by either patient or physician. This is true even of indigenous psychotherapy in Japan: Murase says of *naikan* therapy, "it is not necessary for the counsellor to achieve a full, empathic understanding of the client's intricate inner world. The counsellor accepts and respects the client as a person who has potentially to realize himself."[43] Responsibility for healing is left very much in the hands of patients and their families; physicians are skilled and sympathetic technicians who, even though powerful and in a dominant role, use "soft rule" and allow patients to maintain a sense of autonomy and control. Perhaps because of these attitudes, it is customary for a physician to tell the family and not the patient about a poor prognosis.[44] Malpractice suits are rare in Japan, and this too is probably due to the nature of physician-patient relationships.

Somatization and the Meaning of Illness

There has never been a split between psyche and soma in Japanese thinking and both physicians and patients readily attribute nonspecific somatic complaints, symptoms of depression and other "psychosomatic" symptoms to "stress." An exploration of the principal factors contributing to stress will usually lead one rapidly to a concern about interpersonal relationships within the family or at work, but this concern is expressed in an abstract or neutral fashion, and only very rarely will patients make a statement about their personal situation or feelings. The restraints of "ritual" behavior and communication do not allow one to express what is *uchi* ("within," in this case, within the family) and this approach is reinforced by Confucian mores. Illness is interpreted as an expression of stress at the social level but, because harmony is highly valued and the forms of social behavior and distribution of power cannot be questioned easily (and take primacy over the individual), then a person must adjust for harmony to be restored. Japanese patients, therefore, seek out medication to assist them in their adjustment; if physical order is restored, then, because psyche and soma are indivisible, emotional balance will return. Family, employer and friends can be very patient and supportive during this process and insurance companies allow very long stays in hospital.[25] The ultimate objective of therapy is not to provide symptom relief but to facilitate reintegration into one's own social role—the group must be healed, even at the expense of the emotional well-being of its participants.

Mental Health and Therapeutic Techniques

There has never been in Japan a concept of mental health as separate from health in general until recent years. There are several indigenous psychotherapeutic systems, but the emphasis of treatment is on insight attained through techniques of introspection *(hansei)* and meditation. An underlying premise in the practice of *hansei* is that a "misfocused mind is overly self-focused, selfish. The strategy of therapy . . . is to refocus attention away from the everyday self-consciousness."[45(p103)] Introspection is guided by a therapist in such a way that a patient is supposed to come to an understanding of how he or she can adjust behavioral patterns to suit the given reality of the social world.

Avoidance of a verbal analysis of one's emotional states and negative feelings about others is reinforced through communication patterns in Japan. Neither in "intimate" nor "ritual" communication should one express negative feelings and there is, therefore, usually no acceptable time to verbalize such feelings.* Beliefs derived from Buddhism reinforce this situation because high priority is given to inductive and intuitive learning rather than to deductive analyses and it is also thought that verbal statements cannot possibly express the complexity and changeable nature of one's inner self.

These ideas affect the practice of biomedicine in Japan where somatopsychic medicine is an important specialty in which the techniques of biofeedback, autogenic training, behavior modification, fasting therapy and yoga are very popular even for such complex problems as anorexia nervosa and chronic pain. Ikemi and

*Schooler and Caudill found a 39% greater chance of schizophrenic patients in Japan who were admitted to hospital having been assaultive before admission as compared with those in the United States. They attribute this to the high priority placed on decorum in interpersonal relations.[46]

Ishikawa have stated why they believe somatopsychic therapy to be more effective than psychotherapy:

> The stimulation of somatic awareness can clearly elicit psychic awareness, which may prove to be a more powerful process than the reverse process, commonly known as 'psychosomatics.' According to Oriental thought, self-identification is a process that is based upon an awareness of body feeling which is directly in touch with nature and under its command. Such a self-identification helps the maintenance of lucid sensory awareness and an actual feeling of the law of nature in one's own body, an understanding which is qualitatively different from conceptual understanding.[47(p320)]

DeVos addresses the issue of why psychoanalysis is not popular in Japan. He states that "psychoanalysis has, as its basic premise, the autonomy of the individual. Autonomy is an awesome concept. It can imply that the individual can create personal meaning for himself independent of social considerations; that the mind can divest itself of its own emotional heritage."[48(p123)] A Japanese therapist seeks to help a person adjust to a given social situation, however intolerable it may appear, by helping the patient to achieve more social integration and more self-control. As DeVos notes, "any therapy seeking critically to examine family failure in Japan cannot be popular." If family history and dynamics are explored at all, then it will be done, not to expose "the truth," but to create a positive myth in which past happiness, harmony and loving care received are woven so tightly together that negative feelings, especially anger, do not trickle through. Because there is no concept of duality between mind and body it is possible in therapy in Japan to manipulate both somatic and psychologic variables in the belief that this will help maintain a stable social order.

North America and the Sense of Coherence

There are some obvious ways in which second *(nisei)*- and third *(sansei)*-generation Japanese in North America appear to be highly assimilated: use of the English language, residential dispersion, exogamy (almost 50% of *sansei* are married exogamously in some areas[14]), educational levels and entry into a wide range of occupational categories.[49] But the findings of Kitano and Kikumura,[50] Connors[51] and Woodrum[52] all show retention of a cultural distinctiveness and identification. This is most notable in the areas of family relationships[53,54] and in terms of achievement for the sake of others.[54] Moreover, among *issei* (first-generation immigrants) 65% of a Chicago sampling state that they have daily contact with at least one of their own children.[55] Psychological testing shows that *sansei* college students score close to Japanese college students on qualities such as affiliation, nurturance, abasement and endurance, significantly higher than white students, but they score lower than white students in areas of autonomy and dominance.[51]

Affiliation with larger ethnic social groups is also important for both instrumental and expressive purposes: of 2,304 *nisei,* more than 50% reported that another Japanese-American assisted them in getting a job, as did 58.8% of 802 *sansei.*[52] Despite their high levels of education and apparent assimilation, college-educated Japanese-Americans systematically receive less prestigious employment and less financial compensation than similarly qualified whites.[52] This finding probably represents continued racial discrimination, but it could also indicate cultural factors influencing career choices.

The Japanese heritage of a multilayered social structure and personality appears to have persisted in North America; "making the strange familiar" through the selected use of a pluralistic value system facilitates an effective process of adaptation, while enabling a fostering of a sense of coherence. It is perhaps the people who relinquish this pluralistic approach who become most vulnerable to coronary heart disease.

Health Care for Japanese and Japanese-Americans

In 1980 some 5,000 immigrants came from Japan to the United States[15] and the number of Japanese residing temporarily in the States is increasing year by year; in addition many Japanese-Americans apparently retain certain values that will influence their attitudes towards health and illness in characteristic ways.

The great importance attached to harmony at the social level and the sanctions against verbalizing negative feelings about family members mean that family therapy is unlikely to be successful with Japanese (family medicine and family therapy, as they are practiced in North America, are virtually nonexistent in Japan). Furthermore, even with individual patients, the restrictions imposed by the use of "ritual behavior" between physicians and patients means that social and psychological dimensions of health and illness problems cannot be investigated in an intense and personal fashion. Since, however, social and psychological factors are generally believed by Japanese patients to contribute to illness problems, these parameters can be explored successfully in an abstract fashion by using hypothetic examples. A patient is likely to relay this information in its abstract form to family members. Both patient and family will then privately reinterpret what they have heard into a personal idiom and behavioral changes may ensue. This approach is used very successfully in the practice of traditional East Asian Medicine in Japan. The traditional medical system (including the use of acupuncture, herbal medication and massage) is at present undergoing an extensive revival[25]; emphasis in this system is on a somatopsychic approach, though the social and psychological origins of problems are acknowledged.

Encouragement of contact with Japanese community resources can also provide social supports and perhaps precipitate behavioral changes within a family, but neither the community nor the family itself is likely to introduce any radical changes into the family structure. Persons who appear to be expressing the need for more autonomy through somatization are unlikely to gain more than a brief respite until their symptoms are

brought under control and "harmony" is restored. There seems to be no way for a physician to break into the tight bonds of an enmeshed Japanese family, particularly since the family believes that a physician has no right to try to do this. Moreover, potential guilt that can be induced by encouraging the expression of intrafamily hostilities in Asian families is so great that it is questionable whether it should be attempted at all.[56] The only acceptable ways for a person to deal with intolerable family conflict are through retreatism (leaving the family completely) or some extreme form of expressive behavior such as a suicide attempt. Under these circumstances, if the conflict can be absorbed and tolerated, then a person is expected to do this until it is totally unbearable, even if it means patching up the body to stand more stress. It is very common, therefore, for Japanese patients to seek medication for a wide range of daily problems and for physicians in Japan to dispense it in large quantities. If a physician does not prescribe medicine but seeks to stress the social and psychologic aspects of a case, then a patient is likely to feel dissatisfied and seek help elsewhere. The use of placebos may be one answer to this dilemma. A complementary approach could be an attempt to foster those values that lead to coherence in the life of a patient. This will probably include facilitation of an adjustment on the part of patients to their social milieu by acknowledging the stress in their lives and providing sympathy, but at the same time allowing them to maintain their privacy. It may be difficult for those of us raised in a Judeo-Christian heritage to accept some of the ideas fundamental to East Asian philosophy. Perhaps the most troublesome of all is the idea that primary social groups take precedence over individual needs and autonomy.

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In Search of Healers—Southeast Asian Refugees in the American Health Care System

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Healing is the alleviation of sickness, which includes both medically defined problems of pathophysiology (disease) and personal definitions of not being well (illness). Refugees from Southeast Asia now have a special need for healing because their health problems are changing from those of concern to public health, which are well documented and for which there are known effective treatments, to those that are primarily a personal concern and that are difficult to diagnose and treat effectively because of their chronic nature and their cultural and emotional components. The finding among refugees of physical complaints for which there is no identifiable medical cause is explained by cultural tendencies in Southeast Asia that promote focusing on somatic symptomatology, and by a delayed somatic response to refugee trauma. To prevent escalation of medical intervention, physicians need to be sensitive to Southeast Asians' attitudes toward health and their expectations and apprehensions regarding Western medicine.

Large numbers of refugees from Southeast Asia were first admitted to the United States in 1975. That year of tumult alone brought some 130,000, who were mostly Vietnamese and predominantly professionals, government officials and military personnel who had some close affiliation with the United States and the collapsed Thieu regime. These first refugees were generally well educated (more than 25% were college graduates), young (88% younger than 45 years of age) urban dwellers (75%) of Catholic background (55%) who were in good health and in the company of family (62% arrived in family groups of at least five persons).[1] They were kept in make-shift relocation centers at US military bases where they were given physical examinations[2] and studied English until they found sponsors to assist in their resettlement. Whereas this group of refugees has had to deal with immense psychologic trauma and stress,[3-11] it has not baffled the American health care system to the extent that the subsequent wave of refugees from Southeast Asia has.

The next burst of refugees from Southeast Asia began arriving in the United States in 1979. It reflected the Vietnamese invasion of Cambodia in January 1979 and a new anti-Sinitic policy of the government in Vietnam, as well as new military offenses against the hill peoples of Laos. From January 1, 1979, through February 28, 1983, there were 455,255 refugees from Southeast Asia resettled in the United States, constituting 72% of the total of 631,554 who have arrived since April 1975.[12] This group is so different from the first group and from the general US population that it is usually referred to as "the second wave" of refugees from Southeast Asia. It is heterogeneous in national origin, ethnic identity, religion, language facility, literacy, urban-rural-hill background and health status.[13,14] However, "second wave" refugees are generally less well educated, less literate, less familiar with Western thought and institutions, less facile in English and less healthy than those in the first wave. Escape attempts from the countries of origin were typically long, harrowing and fatal for up to 50% of the displaced; their temporary refuge in camps in Southeast Asia was generally long, even up to seven years, and resources for survival were sparse. Comments in this article generally

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TABLE 1.—*Distribution of Refugees From Southeast Asia in 13 Western States**

State	Estimated Total 28 Feb '83	Percent of Total in United States	Percent of Total in 13 Western States
Alaska	296	0.05	0.10
Arizona	4,045	0.64	1.29
California	228,946	36.25	73.20
Colorado	10,620	1.68	3.40
Hawaii	5,743	0.91	1.84
Idaho	1,297	0.21	0.42
Montana	997	0.16	0.32
Nevada	1,841	0.29	0.59
New Mexico	2,779	0.44	0.89
Oregon	18,113	2.87	5.79
Utah	7,367	1.17	2.36
Washington	30,475	4.83	9.74
Wyoming	266	0.04	0.09
TOTAL	312,785	49.54	100.03†

*From Refugee Reports, 1983.[12]
†Total exceeds 100.00% due to rounding.

refer to this second wave of refugees because of the greater cultural and socioeconomic disparity between them and physicians than between the first wave and physicians.

Half of the refugees from Southeast Asia in the United States have settled in the Western states and a third have become residents of California (Table 1). Four Western states—California, Colorado, Oregon and Washington—have refugee populations that exceed 10,000 in size. Other Western states, particularly Hawaii and Utah, have high refugee-to-general population ratios.

The refugees in the second wave were screened for major public health problems (tuberculosis, syphilis, leprosy and drug addiction) in refugee camps in Southeast Asia. Many were screened again after their arrival in this country, generally by health departments concerned with protection of the public's health. In consequence, a high prevalence of certain infectious diseases has been well documented (hepatitis B, intestinal parasitism, malaria and tuberculosis).[13-28]

Turning Point

We are now at a turning point in the health care needs of refugees from Southeast Asia. The infectious diseases that have been highly prevalent among them are generally under control, if not eliminated. Now refugees are seeking help for more chronic illnesses that are a personal, rather than a public, threat to health and that are not as easily identified or controlled as the infectious diseases. And now, sufficient time has elapsed for signs and symptoms of the posttraumatic stress disorder[29] to emerge.[10,30,31] The chronic personal and emotional problems that are now surfacing demand effective physician-patient communication and a far greater degree of mutual understanding than is necessary for the diagnosis and treatment of infectious diseases.

A large proportion of the adults in the second wave of refugees, however, speak only minimal English, know very little about our health care system and continue to take care of their health as they did in Southeast Asia where few had access to biomedical health care. At the same time, they are so widely dispersed in the United States that in many areas they do not compose a critical mass necessary for inauguration of special services such as modified hospital diets, language banks of trained bicultural interpreters and English language training. This means that caring for them takes time and can be fraught with the frustrations of noncomprehension and "noncompliance."[32] It also means that healing must replace curing in the care of refugees from Southeast Asia.

The Need for Healing

What is the difference between curing and healing? In making a distinction, medical anthropologists differentiate between the terms disease, illness and sickness. *Disease* is defined as abnormalities in the structure or function (or both) of bodily organs and organ systems. *Illness* refers to a person's perceptions of disease and other debilitating conditions. *Sickness* is often used as a cover term for both disease and illness,[33-35] though there is some debate about its meaning.[36-38] *Curing* refers to the treatment of disease and consequently to the practice of biomedicine. *Healing,* in contrast, refers to the alleviation of illness or sickness, and may or may not refer to a diagnosed disease. The extent to which healing occurs in the practice of biomedicine depends largely on the behavior of a practitioner-physician. That is, physicians may believe they are successfully managing the progress of a disease but may still be unsuccessful in dealing with the debility and feelings of illness that persist for a patient. We now understand that this seeming paradox is often related to differing concepts of health, sickness and appropriate health care among members of strikingly different sociocultural groups.

Major Nonbiomedical Concepts of Sickness and Health Among the Refugees From Southeast Asia

Religion and Medicine

While the underlying major traditions are not directly related, there are parallels between paradigmatic schools of thought in the history of Western medicine and medicine as practiced in Southeast Asia. Just as in ancient Egyptian and Mesopotamian medicine, the practice of medicine for some refugees, particularly the non-Christian Mien (sometimes called Yao) and H'mong (sometimes called Miaw or Meo) who come from the hills of Laos, is inseparable from religion. Sickness is believed to come from the wrath or wiles of gods. A physician, then, is a priest who negotiates with the gods (note: not with the patient) to remove or alleviate sickness. A physician-priest is believed to have superhuman powers because of her or his capacity for influencing the gods, whereas the gods are blamed in the event that a patient fails to recover, thereby preserving the reputation of and need for a priest-healer.[39-42]

There are few Mien or H'mong shamans in practice

in this country, which is a radical change not only from the life-style in the hills of Laos, but also from coping strategies used in the refugee camps in Thailand. Conversion to Christianity has eradicated some of the practice, and urban apartment living in heterogeneous neighborhoods has suppressed most of the rest, as calling the gods in H'mong or Mien style involves noise-making that could bring untoward attention to the presence of the refugees and their alien behavior.

Although shamans are rare in the United States, the heritage of belief in external causes of health and sickness persists. It is manifested in the Lao hill people's mistrust, fear and incomprehension of biomedical invasive procedures, whether they be for diagnostic, palliative or curative purposes. Often the best physician is defined as the one who intrudes on the body the least. For example, when given the choice, pregnant H'mong and Mien women almost invariably ask *not* to be given anesthesia during labor and delivery, or they simply avoid hospitals that have a reputation for using anesthesia indiscriminately. There is variation by ethnic group in the degree to which medicine is associated with religion and to which medical intrusion in the body is shunned. Vietnamese women, for example, usually ask for anesthesia during labor and delivery.

Natural Medicine

Southeast Asian refugees, even those in the second wave, are culturally diverse. The Mien and H'mong just described are tribal people from the hills of Laos with predominantly shamanistic systems of belief, though aspects of other systems, such as the use of herbal remedies, may be incorporated. Other refugees come from peasant agricultural villages where medical belief systems are somewhat different, and fewer shamanistic elements are present.

The primary system prevailing among these peasant people is here called *natural medicine,* in contrast to the supernatural medicine of the hill people. The peasant medicine of Southeast Asia is similar to Hippocratic medicine of the first five centuries BC in that both are grounded in a belief in the healing power of nature. Human anatomy, according to Hippocratic-peasant medicine, is composed of bodily humors, and their natural environment, not the gods, determines the extent to which they are in harmonious equilibrium—that is, healthy. Diagnosis in this framework involves observation of the physical and social environments of a patient, and treatment consists of either surveillance while natural recuperative powers are at work, or support for natural vegetative processes such as digestion and sleep.[42]

The Hippocratic-peasant framework is evident in the daily behavior of many of the refugees from Southeast Asia. Growing herb gardens for making herbal medicines is common practice among the H'mong, and massage, tonics and avoidance of excesses are common health maintenance behaviors throughout lowland Southeast Asia (that is, among the Chinese, Khmer, Lao and Vietnamese). An expectation that nature will cure and a fear of invasive procedures may explain the lateness with which refugees tend to present themselves for medical care of blatantly pathologic disorders.

'Hot-Cold' Theory

The tenets of Aristotelian medicine also have parallels in Southeast Asian concepts of health and sickness. The belief that living matter is composed of four elements, air, fire, water and earth, and that each has an associated characteristic—cold, hot, wet and dry, respectively—is common to both Aristotelian and Southeast Asian metaphysical systems and underlies much of Southeast Asian self-care behavior. For example, refugee women who give birth in the United States usually refuse to take baths, wash their heads or drink juices or water in the postpartum period from fear of upsetting the balance of "hot" and "cold" in their bodies. The underlying logic (which might not be as widely known as the practice it generates) is that blood, which is the fire element that is characteristically "hot," has just been lost through delivery; consequently, the body is at risk of becoming too "cold" or getting too much "air," so the above exposures to cold things that are associated with air are avoided.[43] Similarly, when a person is febrile, fluid intake is commonly restricted, the body is dressed warmly and fresh vegetables and fruit are avoided. The underlying logic here is that the body is already losing too much heat, so every effort must be made to retain it: foods that are classified as "cold" (most vegetables and fruits) must be avoided, in favor of foods classified as "neutral" (rice, eggs, chicken broth, teas and sweets).

Resistance to venipuncture is common among refugees from Southeast Asia for a complex of reasons besides the fear of upsetting the "hot-cold" balance of the body. These include the lack of a tradition of blood drawing for medicinal purposes, coupled with its recent association with the military's need for blood: some refugees think that blood is taken from them to give to American troops. Also, although blood is viewed as a vital element of the body, less well-educated refugees may not be aware that the body can compensate for the amount lost and produce more blood.

The fundamental position of the "hot-cold" belief system is shown in self-care behaviors common among refugees from Southeast Asia, be they educated elite or preliterate hill farmers. Western or biomedical medicines are generally classified as "hot" and are perceived as very potent, often too potent for Southeast Asian physiology. Although refugees from Southeast Asia expect to receive medicine whenever they visit a physician, many will adjust the dosage downward to protect themselves from untoward effects, or stop taking it altogether if there has been no relief of symptoms within a few days.[44]

Another common manifestation of the "hot-cold" belief system in refugee self-care behaviors is the dermabrasive procedures.[45-47] These are important self-care practices that are widely used, particularly among the Khmer from Cambodia (now Kampuchea) and

Vietnamese, to alleviate a wide variety of symptoms (headache, myalgia, nausea, cough, backache, motion sickness and so forth). Although they abrade the skin, such minor scrapes are rarely harmful and help persons gain a sense of control over their ailment. Cutaneous hematomas are sometimes purposefully created over the affected area (of the face, neck and anterior or posterior torso, excepting the genitals) to release the excessive "air" that is associated with certain ailments. The hematomas are made in several ways: by firmly pinching the epidermis and the dermis between two fingers while pulling on the skin; by rubbing an oiled skin with the edge of a coin, spoon or piece of bamboo, or by placing a cup from which the oxygen has been burnt out over the affected area for 15 to 30 minutes; as the air in the cup cools, it contracts and draws the skin and "air" up and out, leaving an ecchymotic area on the skin. Some care must be taken when the patient is a child to differentiate these signs of home treatment from evidence of child battering.[47]

Mental Illness

Any of the above concepts of sickness may pertain to emotional as well as to physical sickness. Unmistakable emotional disturbance, however, is usually attributed to possession by spirits of malicious intent; to the bad luck of familial inheritance, or, for Buddhists, to bad karma accumulated by misdeeds in past lives. Partly because of its attribution to immoral causes, mental illness is commonly feared and denied. Disturbed persons are usually harbored within their family unless they become destructive, at which point they may be admitted to hospital (and "forgotten") or otherwise restrained, but at the great cost of bringing shame to the family. Perhaps in consequence, refugees from Southeast Asia who are having emotional problems tend to present themselves for care with physical problems[31] and to avoid referrals to mental health clinics, psychotherapists or psychiatrists.[30] The tendency to somatize has, however, been documented for other groups of refugees as well.[48,49] Generally, a label that does not suggest mental illness such as "family counselor" is more acceptable to Southeast Asians than terms such as therapist, and they will feel most comfortable if given some tangible treatment such as a prescription for medicine. Placebos are widely used by practitioners in Southeast Asia in recognition of patients' expectation of receiving medicine and their usefulness in establishing rapport with a patient.

Nevertheless, an apparently increasing number of refugees are being diagnosed as having psychiatric or psychosomatic problems. The prevalence of appreciable psychiatric problems among adults was reported as 10% in 1980[14] and as 17% in 1983 (for different and unmatched populations).[50] Depression and anxiety were the most common diagnoses, but psychosomatic disorders, tension headaches and psychosis were also found. The prevalence of depression among Vietnamese refugee patients of one medical outpatient clinic was found to be 40%.[51] In a study of refugee (89% Vietnamese or Chinese-Vietnamese) psychiatric patients in Ottawa, more than two thirds were diagnosed as having anxiety or depression (or both), 16% as having a psychosis and another 16% as having adjustment reactions. The difference between the diagnoses and the presenting problems is pronounced: only 12.5% presented with anxiety or depression, whereas 30% were seen because of somatic complaints and 11% for suicide attempts; other presenting problems included hallucinations, school problems, aggressive behavior including wife and child abuse and agitation.[31] Agencies working closely with refugees of any ethnic group from Southeast Asia uniformly report depression as the most pressing problem.[30] While a depression rating scale has been developed for use in clinical practice with Vietnamese clients,[51] there are as yet no such instruments for assessing the mental state of other Southeast Asian refugees.

Somatic Response to Stress

An increase in the prevalence of depression can be expected to continue for at least two reasons: the actual occurrence of depression is probably increasing due to the latency effect of posttraumatic stress disorder among refugees,[52-54] and to an increase in reporting due to greater refugee familiarity with and use of the American health care system. The rising prevalence of depression can be expected to be associated with an increase in refugee health care-seeking behavior that is focused on somatic symptoms. However, the physical phenomena through which the refugees manifest sickness do not necessarily have biomedical equivalents. Examples that are likely to be encountered include the complaint of being "hot": it usually does not refer to a febrile condition and can occur in the absence of fever. Instead, it might refer to a variety of problems, such as flatulence, constipation or dark urine. Other examples are syndromes associated with specific organs: a "weak heart" refers to palpitations, dizziness, fainting or panicky feelings; a "weak kidney" refers to impotence or sexual dysfunction; a "weak nervous system" refers to headaches, malaise or inability to concentrate, and a "weak stomach or liver" refers to indigestion.[44]

What appears to be occurring is a delayed somatization of response to the experience of being a refugee. Because this experience is cumulative, each new experience can complicate and postpone resolution of previous experiences. The refugee experience of trauma can be classified according to stages in the refugee life history (Figure 1).[55] The actual or threatened experiences of persecution and the witnessing of atrocities that occur in a refugee's country of origin are related to the emergence of the posttraumatic stress disorder in the country of refuge or later in the country of resettlement. Meanwhile, a refugee often has been separated from or has lost family members, but might not have been able to mourn their loss because of uncertainty about their fate, uncertainty about his or her own fate, preoccupation with survival or denial. Losses

Components of Refugee Trauma by Stage of Refugee Life History	Emotional Response	Somatic Response
Country of Origin		
Persecution; forced migrations; witness to human-perpetrated atrocities; separation from or loss of family members		
Country of Refuge		
Limbo experience of finding asylum and of refugee camp life; separation from or loss of family members; hasty marriages and affiliations with new families in refugee camps		
Country of Resettlement		
Resettlement in an alien culture (USA) where religion, language and skills may no longer be relevant and previous social support system may not exist	Anxiety Delayed grief Depression Posttraumatic stress disorder	Psychosomatic conditions Somatic problems with no identifiable cause
Frequent isolation from compatriots		
Low English-speaking ability		
Wrong skills for American economy: cannot find jobs; welfare dependency		
Children more skilled than parents: parent-child role reversal and tension		
Marital conflict; single parent-headed households		

Figure 1.—Model of delayed somatic response to refugee trauma.

that require grieving can accumulate overwhelmingly fast in the life of a refugee. Complicating these experiences is the risk of mismatch in new alliances that are hastily formed in refugee camps to gain companionship. Subsequently there may be myriad incongruities between a refugee's knowledge, skills and expectations and the expectations of the new environment in the country of resettlement to wound a battered psyche even more.

It should be remembered that the origins of some emotional responses and some sicknesses of refugees predate or are otherwise unrelated to refugee trauma. Refugee trauma, however, increases the likelihood of specific emotional responses such as anxiety, depression, delayed grief and posttraumatic stress disorder.[53,54] Cultural heritage and the social environment then shape the nature and extent of somatization of the emotional response. We do not yet have data that identify variation in the type of somatic response to stress among the different ethnic groups of refugees from Southeast Asia, but we do have reports of somatic complaints that have no medically identifiable cause.[31]

Implications for the Physician-Patient Relationship

When the above model of delayed somatization of refugee trauma pertains to a refugee patient's sickness, the cause of the sickness—refugee trauma—cannot be cured or mitigated by medical ministration alone. Consequently, the sickness might persist despite expert symptomatic treatment, or it might disappear, reappear or metamorphose for no apparent medical reason. This can be exceedingly frustrating for a physician and can be guilt-provoking when, with the best of intentions, the physician pursues an intractable symptom with progressively intrusive measures, only to have it persist with stunning recalcitrance.

The danger of escalating intervention beyond what proves, in retrospect, to be medically indicated and the danger of misdiagnosing signs of chronic disease as delayed somatic response of refugee trauma can be prevented by assiduous attention to a refugee patient's point of view. This means, for example, respecting a Southeast Asian's fear of bodily intrusive measures by keeping them to a minimum. It also means probing beyond the smiling "yes yes" response that is, for Southeast Asians, the proper way to show respect for another person, to determine a patient's understanding of the matter at hand. This might require the assistance of a trained bilingual interpreter.[32] It does require that the physician or nurse ask a patient to repeat what has been said about the nature of the problem, about what should be done for it, how long it will take, what specific medications the patient took, what measures the patient has considered taking to deal with the problem and so forth in order to validate a communication. It also might require authoritative suggestions of hope, prescriptions for benign medicines when others are not medically indicated, encouragement to continue taking home remedies such as herbal teas and poultices or to continue consultation with an ethnic healer,* and it might require allowing a patient to return for consultation even when medical remedies have been exhausted.

The risk of fostering medical dependency probably will fall over time as an increasing number of Southeast Asians become health care professionals, able to minister directly to the illnesses and diseases of fellow refugees by virtue of their common cultural background and history as refugees. Meanwhile, the risk of medical dependency can be therapeutically justified because somewhat extended health care provides an arena where a refugee can feel validated as a patient and secure in the repetitive care of an authority figure—the physician—whom she or he perceives as having the power to heal.

*In a study of biomedically trained physicians in northern Thailand, two thirds estimated that more than half of their patients were using herbal medicines or receiving treatment from practitioners of indigenous medicine (or both): "They also estimated that approx. 90% of their patients had sought medical care only after trying herbal medicines and/or attempting self treatment with the aid of drugs and medications purchased from drug sellers."[55]

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Popular Medical Concepts in Jamaica and Their Impact on Drug Use

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Universally, popular medical concepts form the basis of lay understanding of health, disease and cure. In Jamaica these concepts first developed in association with traditional herbal medicine. Now they are applied to the most common forms of primary care: over-the-counter and prescribed drugs. Research findings suggest that where there is disagreement between popular and professional medical models, as is the case in Jamaica, the effect of popular concepts is to increase self-medication and reduce adherence to prescribed medical regimens. To ameliorate this situation and the attendant potential risks for drug consumers, methods for providing needed drug information and improving physician-patient communication are suggested. These suggestions apply not only to Jamaicans living in Jamaica and the United States, but also to members of any group whose ethnomedical concepts differ from the biomedical training of physicians.

Universally, lay—or popular—concepts of disease etiology and therapy form the basis of most people's understanding of health, illness and the curing of disease. These concepts address and attempt to explain several important aspects of illness:

- etiology,
- time and mode of onset of symptoms,
- pathophysiology,
- course of sickness and
- treatment.

In the extent to which they attempt to answer some or all of these concerns, conceptual systems differ considerably cross-culturally.[1]

Underlying popular medical concepts is a logic that directs reasoning along certain lines. An example of this is believing (as in American popular medicine) that the relationship between symptoms and treatment should be allopathic; that is, that medicines should produce effects different from those of the disease being treated. Popular medical concepts are also adaptable, and both pliant enough to cover a wide range of experiences and imprecise enough not to be refuted by specific instances that appear to contradict their logic. In this respect their character differs significantly from the more formalized tenets of scientific medical knowledge.[1]

This article will focus on the impact of popular medical concepts on modern drug therapy, using ethnographic data gathered in Jamaica. Fifty years ago most Jamaicans used traditional plant medicines for primary medical care. Today most of the population gets its primary medical care at health centers and community pharmacies. As a result popular medical concepts that developed in relation to traditional substances are now applied to drugs prescribed by physicians and to over-the-counter (OTC) drugs purchased for self-medication. The patterns of prescription and OTC drug use that have resulted from this major change suggest that in Jamaica popular concepts have the effect of discouraging adherence to prescribed drug regimens and encouraging self-treatment with drugs. In the process consumers run the risk of drug misuse, drug-drug interactions and neglect of serious medical conditions.

The findings reported for Jamaica also apply to the estimated 254,000 Jamaicans living in the United States. The elderly and recent adult immigrants are

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particularly likely to subscribe to popular concepts and to weigh therapeutic decisions within their framework. Jamaicans born in the United States, or who have received much of their education here, are less likely to express these concepts openly but they may follow some of the practices associated with them at home. Even second generation Jamaican-Americans may subscribe to some traditional medical concepts, especially those which do not conflict significantly with scientific medical practices. Physicians working with members of other Caribbean immigrant populations such as Haitians and Bahamians, whose medical conceptual systems closely resemble those of Jamaicans, can expect similar approaches to defining health and illness and similar responses in evaluating medical treatment.

At a broader level, similarities between behavior observed in Jamaica and behavior reported in the United States and other settings point to general patterns which emerge when traditional or popular medical standards are used in the context of modern biomedical technology to evaluate symptoms and regulate utilization of mainstream medical services and adherence to treatment regimens. Examination of these patterns shows a need for better communication generally between physicians and patients and in particular for greater awareness of ethnomedical concepts among physicians working with immigrant and minority patients. The article concludes by discussing how improved communication of information can be used to achieve safe and effective drug use.

Jamaica

Jamaica is the third largest island in the Greater Antilles and part of the chain of islands forming the northern limit of the Caribbean Sea. Located about 90 miles south of Cuba and 600 miles south of Miami, it is approximately 140 miles long and 50 miles wide. Its area is 4,207 square miles, making it about the same size as the state of Connecticut. In 1979 the population was estimated at 2.2 million, of whom 70% were urban, living in the capital, Kingston, and other towns, and 30% were rural.[2,3] Of the population 90% is classified as African (that is, of West African descent), 6% as Afro-European and the remaining 4% as East Indian, Afro-East Indian, Chinese, Afro-Chinese and European.[3]

Originally Jamaica was inhabited by Arawak Indians, but by the time the British captured the island from Spain in 1655 the Arawaks had been completely killed off and Jamaica was inhabited only by a few thousand Spaniards and a few hundred West African slaves. From 1655 until the emancipation of the slaves in 1838 Jamaica's development was dominated by sugar and the plantation system. With the growth of the plantation economy in the 17th century the population changed rapidly. By 1673 blacks, who had been imported in massive numbers to work on the sugar plantations, began to outnumber whites.[4] From that time onward Afro-Americans of West African descent made up most of the Jamaican population.

TABLE 1.—*Ten Chief Causes of Mortality in Jamaica, All Ages, 1977**

Disease	*Deaths Per 100,000 Population*
Cerebrovascular disease	93
Heart disease	90
Malignant neoplasms	77
Hypertensive disease	35
Influenza and pneumonia	32
Diabetes mellitus	26
Enteritis	24
Accidents	17
Perinatal mortality	15
Bronchitis, emphysema, asthma	12

Source: Jamaica National Planning Agency: Economic and Social Survey (1979). Kingston, Jamaica, The Government Printer, 1980

*"Ill-defined" causes excluded (rate=57/100,000).

With emancipation (1838) the black slave majority became an independent self-sufficient peasantry whose economic base was the production of small-scale agricultural crops for both export and domestic use. Today agriculture is still an important part of the Jamaican economy, but it is no longer its central feature. Bauxite mining, tourism and light industry have also become significant. Compared with other developing nations the standard of living is relatively high, with per capita income estimated at US$1,304.[5] Unemployment is also high, however, and there are enormous gaps between the life-styles of the rich and the poor. Some 26% of the labor force was unemployed in 1981, with numbers reaching 42% for young people and 39% for women of all ages.[6] Emigration is also high, almost half a million people having left Jamaica permanently in the last 20 years to settle in Canada, Britain and the United States.

The Jamaican population is strongly divided by social class. The society can be described as a pyramid with a broad base of unemployed people, poorly paid workers and small farmers and a small apex comprised of the wealthy elite. Income distribution is highly uneven as employment figures suggest, with 5% of the population earning 30% of the income in 1978 and 20% of the population earning 2.2% of the income.[2]

Mortality and Morbidity

In 1977 (most recent statistics available) the chief causes of death in Jamaica for all ages were chronic diseases, accidents, respiratory diseases, causes related to perinatal mortality and enteritis (Table 1). The overall death rate was 6.4 per 1,000 population while the infant mortality rate was 18.5 per 1,000 live births. Life expectancy for the 1980s is projected at 71.5 years. Although the early neonatal death rate was probably underreported, infant mortality on the whole dropped appreciably during the 1970s, from a high of 30.9 per 1,000 in 1972 to its present level which is well below average for the Caribbean and Latin America. During the decade chronic disease and respiratory disease death rates increased, as did motor vehicle

accident death rates (also probably underreported). Death rates from enteritis and malnutrition declined.[6]

Among infants and small children the most frequent cause of mortality is malnutrition, while in young adults accidents account for most morbidity and mortality. In the population over age 45 chronic disorders such as vascular disease, diabetes and cancer, along with pneumonia, are the chief causes of death.

Morbidity rates for communicable diseases have dropped in recent years as a result of immunization and vaccination programs, but the following diseases continue to be major causes of morbidity: dengue fever, venereal diseases, tuberculosis of the lungs, influenza, pneumonia, measles, tetanus and typhoid.[6,7] The incidence of venereal diseases is especially high in the sexually active 15 to 45 age group. In general, with the eradication of yaws in the 1950s and malaria in the 1960s and the successful lowering of the rate of hookworm infestation in the 1920s, the health problems of Jamaica have come to resemble more closely those of the United States and Europe than those of other developing countries.[8]

Popular Concepts of Health, Disease and Cure

Popular medical concepts tend to be identified with the Jamaican lower class because this group expresses them most explicitly but to some degree they are held by virtually all Jamaicans. They are a mixture of West African philosophy, Hippocratic humoral concepts and the concept of "germs," with germ theory appearing to be the weakest element. They are used to explain the cause of illness, to determine the most appropriate treatment and to evaluate the effectiveness of past or present therapies.

Health

Health for most Jamaicans is defined by specific physical signs, namely having a good appetite, feeling strong and energetic, being "fit" rather than *maigre* (thin or scrawny) and being able to accomplish daily activities without pain or other physical difficulty. In both men and women health has sexual as well as physical connotations. A healthy man is not only physically strong but he is virile, as shown by his ability to drink heavily, to be sexually active and to father many children. A healthy woman is strong, well-built and fertile. Health in children is associated with activity rather than strength, and with freedom from coughs, colds, diarrhea and other overt signs of disease.

Absence of one of the signs of health is not necessarily an indication of illness—for example, people can "feel low" and listless without actually being considered sick—but it is a signal that unless preventive action is taken illness may eventually result. Bleeding and pain are two signs that are invariably interpreted as indications of disease.

Concepts of Disease Etiology

Most illnesses are believed to be caused by (1) "cold," (2) "gas," or "wind," (3) "heat," (4) "bile," (5) blood imbalances or (6) germs. Etiological explanations involving heat, cold, bile and gas/wind are applied mainly to symptoms in which there is a feeling of pain, heat or chill or there is a discharge; those involving imbalances of the blood are applied to internal conditions and changes in the skin; those involving germs are applied primarily, but not exclusively, to venereal diseases. These associations and their manifestations in specific symptoms are shown in Table 2.

- *Cold* is the result of experiencing a sudden change in temperature, "catching a first draft" or getting wet. Its symptoms are discharges, pus, phlegm and mucus in any part of the body. To prevent "cold" people avoid going outdoors when it is raining, keep their heads covered as much as possible (especially older women

TABLE 2.—*Associations Between Etiological Agents, Parts of the Body, Symptoms and Appropriate Types of Medicine*

Agent	*Associated Parts of Body*	*Associated Symptoms*	*Appropriate Medicine*
Heat	Belly; body in general	Belly hot; fever; "pressure" headaches	Purging (belly hot): harsh laxatives Cooling: toilet water; inhalers; diuretic beverages
Cold	"Mole" (fontanelle); "stomach" (chest); head; back; womb; eyes; ears; knee, etc.	Phlegm; discharge; arthritic pain	Cutting: laxatives; inhalers; cough syrups Drawing (pain): liniments
Bile	Belly	Bellyache; belly boiling; belly running; biliousness; "feel bad" (nausea)	Bitter and cutting: bitter laxatives; antacids
Gas/Wind	Belly; knee; elbow; other joints	Traveling pain; discomfort; aching; stiffness; arthritic pain	Drawing: salves; liniments; toilet water
Imbalance of Blood ...	Head ("pressure"—i.e., hypertension); skin; general health of internal organs	Bad blood; feel low; bad "circulation"; nerves; rash; bumps; weak blood; sweet blood (diabetes); giddiness ("pressure"); cancer	Building: tonics, bitter or sweet depending on specific symptoms Cooling (pressure only): toilet water; inhalers; diuretic beverages Bitter and purging: harsh laxatives; bitter purgative tonics; bitter antacids
Germs	Genitals	Venereal diseases	Prescription drugs or antibiotics bought over-the-counter

and young children) and generally keep covered in situations where there is a chance of exposure.

- *Gas and wind* are associated with the joints, the back and the stomach. They are manifested in traveling pains: pains that go from the shoulder to the elbow, that travel from one part of the back to another or that cause recurrent stomachaches. The causes of a gas/wind imbalance within the body are less clear-cut than the causes of cold. Sometimes changes of temperature can bring one about, other times it is the result of overexertion, age or bad eating or drinking habits. Gas and wind are more associated with mature adults and the elderly than they are with children because "gas" pains are usually chronic.
- *Heat* is associated with fevers, stomachaches in which the stomach feels hot and painful to the touch and headaches in which the head feels hot and the eyes burn. Through its association with fevers and headaches, there is a link between "heat" and the balance of the blood. This is reflected in such concepts as that blood that is too hot contributes to "pressure headaches" (considered a sign of hypertension).
- *Bile,* in Jamaica, is believed to occur naturally in the stomach rather than the liver. Bile causes problems when it is imbalanced by pregnancy, bad food, excessive drinking or other disturbances. The symptoms of bile are restricted to the gastrointestinal region and include nauseousness, diarrhea, churning of the stomach and stomach pain. Bile tends to produce more painful, acute and disruptive stomach symptoms than either gas/wind or heat.
- *Imbalances of the blood* are the result of not eating the right foods, drinking too much, getting rundown, tension and circulatory problems. Signs of imbalance include "feeling low" and not having any energy; skin rashes, sores and acne; hot, "pressure headaches"; diabetes, and cancer.
- *Germs* are more frequently alluded to by middle class, more highly educated Jamaicans than by the lower class, but even so few medical problems are ascribed solely to this cause, although it may be mentioned as a contributing factor. Most infectious, communicable diseases are traced to one of the traditional causes of disease, even if a medical practitioner has identified a microbial origin. The reason venereal diseases may be so consistently linked with "germs" may be because of their clear symptomatology (in men), the unambiguous manner in which they are communicated and their responsiveness to biomedical treatment.

Concepts of Cure

Symptoms in Jamaican popular medical thought are identical with illness and disease; therefore, if there are none of the signs that are popularly considered to be symptoms of disease it is assumed that a person is well. When symptoms are present, they are the disease itself: that is, a skin lesion is not a secondary sign that a person has the disease called "sugar" (diabetes), the lesion is itself "sugar." By this reasoning the "sugar" is cured if the lesion goes away.

Medicines are administered in accordance with this identity between cause and effect. Their effectiveness is judged in relation to how rapidly and completely they alleviate symptoms and give "ease." The actions by which medicines are thought to work are: "bitterness," "cutting," "cooling," "scraping and building," "scratching," "purging or washing out" and "drawing out" (Table 2). As the terms imply, expulsion of disease-causing impurities is the primary mechanism by which bodily equilibrium is restored. Once the body has been cleansed, healing processes can begin.

The way in which a medicine is thought to eliminate an impurity corresponds for the most part to the appearance or internal sensation of a particular symptom: phlegm, or "cold," responds to "cutting" medicine because once it is cut it can flow or be released from the body; a pain that travels can be "drawn" from the body by massage.

Effects of Popular Concepts on Use of Drugs

Congruence with popular medical concepts is of critical importance for drugs. Medicines, whether OTC or prescription, are considered effective only if they "fit" the illness for which they are intended: if prescribed for "cold" illnesses they should be cutting; if for digestive problems, laxatives; if for the blood, bitter, and so forth. In other words, they should correspond as closely as possible to the associations outlined in Table 2. A medicine that does not meet these criteria is not believed to be effective unless it is supplemented with another that does.

The principle of congruence has a particularly strong impact on the use of prescription medicines because patients exercise no influence on their selection. If a prescription drug is not congruent with popular categories this will directly affect how, or whether, it is used. Problems physicians encounter in the treatment of hypertension are a good example of the impact of not being congruent on a drug's use: hypertension, or "pressure," is thought to be caused by worrying and incorrect circulation of the blood; therefore, it would respond well to "cooling" liquids, which both "cool" the blood and make the person who takes them feel physically cool. Prescribed medication for hypertension, however, is invariably in tablet form, and not only does not impart a cooling sensation but does not have any discernible physical effect. Thus there is no way to tell if it is "working." Because people do not feel any different after they take methyldopa (Aldomet) or other tablets for raised blood pressure, they tend to doubt their efficacy. Some stop taking them, especially if they produce unwanted, unexpected side effects, or change their pattern of taking them. Others continue taking the tablets, but to increase their effectiveness supplement them with cooling herbal teas or with commercial tonic waters or inhalers. The risk here

is that, when wrongly used, drugs to treat high blood pressure may be dangerous.

The therapeutic implications of the principle of congruence, as demonstrated by this example, are obvious: when prescribed medicines do not fit with popular categories of medical action, patients are liable to stop taking them because of concerns about their effectiveness. Some prescription drugs that do not fit into popular categories are saved from being completely discarded by their expense and prestige value. That is, because they are high status medicines that, if prescribed by a private physician, represent a significant financial investment, people are reluctant to stop taking them altogether. Instead they enhance their therapeutic action, as in the example of hypertension, with commercial (or sometimes herbal) medicines in which they have more confidence. This creates a certain harmony from the point of view of popular theory and ensures use of the prescribed medication, but it also puts the consumer at risk of adverse drug reactions and drug-drug interactions resulting from taking combinations of OTC and prescription drugs.

Compared to prescription drugs congruence is less problematic for OTC drugs. First, a variety of products are available, many of which have been tailored specifically to satisfy popular medical tastes. Second, these medicines are self-selected and customers can find out about their properties beforehand from other customers or the pharmacist and clerks. Many OTC tonics are popular precisely because they meet the requirements of a cutting medicine: being dark, bitter and laxative in effect. Antacids that seem especially effective at "cutting" gas and upset stomachs have gained a similar popularity. Any "stomach remedy" that also has laxative effects is bound to be a marketing success because of the importance the culture places on being able to "feel" medicine working and experience noxious wastes being passed from the body.

With OTC drugs there is more likely to be a problem of overuse or inappropriate use, because of apparent congruence with popular medical concepts, than of underuse. People often take these products for purposes other than those intended by the manufacturer because they seem to "fit" these other applications. Antacids are taken for arthritic pains because they "cut" gas, purgatives for abortions because they "cut" the womb, laxatives for colds and flu because they "cut" cold, inhalants for hypertension because they "cool" the head, bitter tonics for diabetes, boils and other sores because they "clean" the blood and restore its balance and antibiotics (bought over-the-counter) to prevent colds and "build" the body. Sometimes these reinterpretations, or extensions, of the uses of OTC medicines are relatively harmless from a medical standpoint but there is an unquestionable potential for medically dangerous results. These could arise if diseases, especially chronic conditions, are neglected by people who think they are treating them effectively; if powerful purgatives are overused in efforts to gain various secondary effects, or if antibiotics and other substances whose administration should be monitored are overused or misused. The following case illustrates some of the risks patients run from misuse of OTC drugs and failure to use prescribed medication.

Report of a Case

Mrs Green (as I will call her*), who is in her mid-60s and lives in a very remote rural settlement, had high blood pressure and diabetes, diagnosed by Dr Stewart, a physician employed at the government health center about ten miles from Mrs Green's community. Dr Stewart put Mrs Green on a restricted diet and also gave her some ointment to apply to her foot, which was painful and becoming leathery. After her visit to Dr Stewart, Mrs Green went to a "bush doctor" (traditional healer) who gave her an herbal treatment for diabetes. After drinking this infusion for a few weeks, Mrs Green went back to Dr Stewart and asked her to test her urine. Because the tea the bush doctor had prescribed resulted in a urine test showing normal sugar concentrations, Dr Stewart told Mrs Green that her test was "OK." Mrs Green took this as a sign that her diabetes was cured.

A few months later, because her foot problem had not improved, Mrs Green went to a private physician, Dr Bell, whose practice is near the health center. Dr Bell did not test her urine, and Mrs Green did not tell him about the earlier diagnosis of diabetes. Dr Bell gave Mrs Lewis a prescription for another type of ointment for her foot. Mrs Lewis told me she was satisfied with the new ointment because it seemed to be working—that is, clearing up the problems with her foot—and she could buy it off the shelf at the pharmacy (also ten miles away). Dr Bell also gave Mrs Green some tablets, to take "when necessary." Mrs Green was never sure what they were for, and since she was not told that she *had* to take them, she never did.

Comment

Mrs Green's case demonstrates the reliance on OTC medicines that can result from the combination of popular medical concepts with poor physician-patient communication. Her brief encounters with physicians cannot really be considered proper medical care, and yet for the poor they are all too often the norm. Mrs Green's initial visit to the health center was probably prompted by the problems she was having with her foot. Since her husband had lost the use of one leg (from diabetes), she probably had some awareness of the possible consequences of neglecting itchy, scaling skin, but it is not clear that she herself knew of the connection between her husband's disability and his diabetic condition. Nor is it clear that she ever understood the connection between her own overt symptoms and the diagnosis of diabetes. It is widely known that there is an herbal tea that changes the results of urine tests for diabetic persons and because symptoms are

*All names are changed in this example.

identified with disease this means that this tea is seen as "curing" diabetes. When Dr Stewart said that the urine test was "OK," this confirmed for Mrs Green that she had been cured. Apparently the physician had not adequately explained to her that diabetes is chronic, or she did not understand or accept the explanation. Dr Stewart must have assumed that Mrs Green's urinary changes were the result of her adherence to the restricted diet, for she seems to have been unaware that there is a tea that gives such results. Given the prevalence of diabetes among older Jamaicans, Dr Bell, the second physician, should have had Mrs Green's urine tested when she came in for her foot ailment but he did not; and since she had formerly been at the health center, he did not have access to her chart. Mrs Green, "cured," not connecting her foot lesions with a "blood" disease and perhaps also testing Dr Bell's diagnostic skills, offered no information other than her obvious symptomatology. It is unclear what the tablets Dr Bell prescribed were for, possibly hypertension, but since she did not understand how they related to her symptoms, she never took them. She was satisfied with the ointment prescribed by the second physician because it was easy to get, and was alleviating what she felt, at that time, to be her major medical problem.

Improving Use of Drugs

It is evident from the case above and earlier discussion that in Jamaica popular medical beliefs play a decisive role in both adherence to prescribed drug regimens and self-medication with drugs. The pattern that is apparent is that if people cannot understand drugs according to the logic of popular principles, then they either reject them or modify them in some way to make them conform to expectations. Harwood reports a very similar pattern among Puerto Ricans in New York City, where conflicts between traditional classifications of medicines and physicians' recommendations are resolved either by administering additional substances that effectively neutralize the perceived adverse effects of the prescribed medication, or by neglecting the physician's recommendations entirely.[9] Logan, describing the acceptance of modern medicine by Guatemalan peasants, reports the same pattern of adaptation. He observes that "patient behavior is predictable as long as, and to the degree with which, the appropriate ['hot/cold'] qualities are known for both the patient's illness and the prescribed medicine."[10]

Studies conducted in Jamaica indicate that inadequate physician-patient communication is an important contributing factor to poor adherence to prescribed drug regimens and misuse of prescribed drugs. One study of 80 patients from two public hospitals in Kingston found that 74% of the sample did not know the effects their prescribed medicine would have. Few had been given verbal instructions on how to take their medicine and most, when questioned, were found to be administering them improperly in some way.[11] In another study, of adult diabetic patients at an outpatient clinic, 77 patients (75% of the total sample of 103) said that at the time of diagnosis the physician had told them they "had sugar," but had given them no other explanation of the nature of their problem. Some 9% said that the physician had told them nothing about diabetes at all. Among the severely diabetic patients there was a significant difference in the control of the disease (through diet and use of medication) between those who said they were given a full explanation of the disease initially and those who said they were told only that they had sugar.[12]

Several factors contribute to poor physician-patient communication in Jamaican health centers and public hospitals. The Bennett and White study found that physicians were deliberately withholding information, that patients did not understand the little information they had been given and that patients were actually not being told about correct medication use (dosage instructions are always written on drug containers but many patients cannot read).[11] The shortage of physicians and consequent overcrowding of patients at most facilities, along with behavioral expectations related to social class which reinforce authoritative roles for physicians and deferential roles for patients, also contribute to the communication problem.

In Jamaica low levels of formal education and a virtual absence of health and consumer education reinforce public ignorance and misunderstanding of basic anatomy and such fundamental concepts as contagion and infection. A similar situation obtains in many low-income and minority communities in the United States, as described earlier in the paper. In order to improve the therapeutic success of prescription drug use and the quality of self-medication, whether in Jamaica or in communities in the United States, changes initiated by providers appear to be the necessary first step. The physician-patient relationship has been identified as a critical source of many problems, but it does not have to be the sole focus in intended changes. Rather a beginning would be better communication of drug information by all appropriate health care personnel, including pharmacists and nurses as well as physicians. This information would include standardized descriptions of how drugs work, what tablets do when they are ingested (for example, some Jamaicans think that they simply accumulate in the stomach) and how to interpret such instructions as "two," "three" and "four times a day," "before meals" and "after meals." This suggestion could usefully be implemented both in this country and in developing countries where popular drug use is increasing. It is not as important to challenge popular medical concepts, or even to question them, as to supplement them with additional information of an objective nature from an authoritative and respected source.

In situations where popular classification of foods or medicines may cause conflict, a somewhat different approach is necessary. First the physician, nurse or

pharmacist who is giving advice must determine if the patient's views undermine the recommended treatment regimen. Then an approach which is satisfactory to both the patient and the practitioner must be agreed upon.[9] The probability of changing a patient's concepts of disease etiology and appropriate therapy is extremely small; nevertheless these concepts can be worked with in the name of improved communication.

When popular concepts are a people's main source of medical knowledge, whether because of language and literacy barriers, poor physician-patient communication or insufficient efforts from sources other than physicians to provide appropriate supplemental advice, self-medication is likely to be favored and adherence to physicians' recommendations to be minimal. The crucial issue to be dealt with is not "noncompliance" per se, but the risks that uninformed use of over-the-counter and prescription drugs and neglect of recommended therapy can pose for unsuspecting adults and children.

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Pacific Islanders—Migration and Health

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Native Hawaiians and peoples from American Samoa, Guam and the Trust Territories of the Pacific Islands are all recipients of US subsidized health care. Categorized as Pacific Islanders they are a heterogeneous group with differences in biology, cultural adaptation to varied ecological settings, historical influences resulting from colonialism and present-day political factionalism. Yet, westernization on home islands and migration to Hawaii and the western United States have created similarities in disease patterns among these culturally diverse peoples. They have high rates of the chronic diseases of civilization: cardiovascular disease, diabetes mellitus and hypertension. Obesity, associated with these ailments, has become a major health problem among Pacific Islanders and may be attributed to changes in local food production and consumption in conjunction with sedentarization. Culturally and linguistically distinct from the American mainstream, these people as migrants or residents are marginal within the US social structure and find if difficult to obtain adequate medical treatment.

To hail westerners as discoverers of the Pacific Islands is inaccurate as well as ungracious. While Europeans were still paddling around in their small, landlocked Mediterranean Sea or timidly venturing a few miles past the Pillars of Hercules, the Oceania "primitives" were moving about the wide Pacific in their fragile canoes and populating all its far-flung islands.[1(p83)]

Pacific Islanders continue to migrate from their homes to distant shores primarily in search of better job opportunities, education and health care. Hawaii serves as a magnet with its entry port status and absorbs thousands of Islanders each year. It provides an island habitat and is a strategic stepping stone for Pacific peoples' migration to the United States mainland. Constituting a group with diverse genetic and cultural heritage, these immigrants are dependent upon subsidized health care for treatment of a wide range of health problems. Provision of adequate health care and hopes for patient compliance among Islanders are areas of current concern for policymakers and health care providers.

This paper is a survey of selected Pacific peoples and a discussion of their health and political status, their patterns of migration to the United States and the importance of cultural identity in their health behavior. It also deals with the heterogeneity of Pacific Islander migrants since both cultural diversity and individual identity play important roles in behavior affecting health.

The Pacific Islands

Oceania contains 10,000 islands within the 30 million square miles of water constituting the Pacific Ocean.[1,2] The immense subregions—Melanesia, Polynesia and Micronesia—probably at one time represented distinct phenotypes and cultural traditions dispersed upon small land areas of the Pacific basin. The history of the Pacific, however, reflects the constant movements and mixing of people, and thus the presence of much diversity. Today, the labels Melanesia, Polynesia and Micronesia merely serve as convenient categorizations of place but not as finite definitions of population groups and cultural practices.

Melanesia, in contrast with the other two areas, generally contains a more dispersed, less centralized population typified by dark skin and frizzy hair. Partly because of its western geographic location, colonial history and non-US political affiliations, few Melanesians migrate to this country. Instead they attend

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school and seek employment or medical care in Australia or Papua New Guinea.

Portions of Polynesia and Micronesia, on the other hand, are politically and economically connected to the United States and, therefore, contribute the largest proportion of Pacific Island immigrants and native populations. The areas of most interest to US physicians include Pacific Islanders in the state of Hawaii, the unincorporated territories of American Samoa and Guam and the Trust Territories of the Pacific Islands (Northern Marianas, Palau, the Marshalls and the Federated States of Micronesia). The peoples of these divergent groups have in common only a history of island living and a present-day similarity in political affiliation, socioeconomic status, high levels of emigration and disease patterns.

Polynesia, home of Samoans and Hawaiians, means "many islands." It once had the most internally homogeneous population, especially in terms of language, culture traits and appearance (fair skins, straight hair and tall, large bodies). Groups as far distant as the Maori of New Zealand and Native Hawaiians constituted a recognizable cultural group. At one time they were large, highly stratified societies. Today these groups, more urban and genetically diversified, have much less in common, partly as a result of differing patterns of assimilation to varying Western traditions. The transformations are reflected in changing disease patterns, especially in the high rates of chronic disease.[3,4] Polynesians long adapted to island ecosystems have started moving away from their island environments without consideration for the future implications to their health.[5]

Micronesia, or "tiny islands," has always had a wide range of cultural and phenotypic groups. Along with Polynesians, Micronesians have a strong eastern Asiatic affiliation and their appearance is varied, with some Polynesian and Melanesian resemblances.[2] Micronesian groups are much less homogeneous culturally than Polynesian societies and the regional political history dominated by a series of foreign powers has created a patchwork effect upon the local populations. In the Caroline Islands, part of the recently formed Federated States of Micronesia, I interviewed a man who identified himself as Ponapean. His father had been a resident German, his mother was Ponapean and he spoke both of their languages. He received his education in Japanese, sent two sons to Japan for school, had learned to prefer sashimi to fish stewed Islander-style in coconut milk, and related his medical history to me in more than adequate English while sipping a warm Budweiser beer.

This is the cultural present. Human groups do not remain cultural isolates caught within old traditions; culture evolves and adapts to changing circumstances. This does not make the particular cultural identity any less important; Pacific Islanders have strong ethnic identities based not only upon pre-European contact heritage, but also upon contemporary life-styles and beliefs. Ethnicity is also bound up in the sense of place. Migration disrupts this; yet the movements of people has dominated the human settlement of the Pacific basin. Pacific peoples often identify with places and trace their origins to settings in remote or mythological time.[6] We must respect this identity bound up in the sense of place even as it transforms before us. This is especially critical within the context of polycultural health care situations in which pride in one's culture may provide psychological well-being and self-respect.[7]

Distinctive effects upon Pacific Island life have occurred during the last four centuries. Intermittent Western medical services were provided during this period of exploration, settlement and defense in the Pacific. Immunization and sanitation campaigns were implemented, but very often when the strategic nature of an island ceased to exist for the colonial power, the foreign administration or navy left the scene. With them went the extensive health care services and Western models of illness and health.

Today access to medical care continues to be limited in the Pacific. A major factor is geographic isolation and extreme distances between inhabited land masses. Areas under US sponsorship, however, have in many cases been improving health care services over the past two decades. Regional health centers have been built with US funding, and policy continues to support this social service as it also supports subsidized medical care. For instance, the Lyndon B. Johnson Tropical Medical Center in American Samoa has special leprosy and tuberculosis units with 181 beds. Guam's facilities include the 200-bed Guam Memorial Hospital and several church-run clinics with very high standards. It serves as a regional medical center for much of Micronesia and the western Pacific.

In each of the state centers of the Trust Territories there are small hospitals and 170 dispensaries distributed on the more remote islands. Almost all of the medical staff are part of the public service, and there are few private doctors. Medical referrals are made to Hawaii's Tripler-Army Hospital and San Francisco, in addition to Guam and American Samoa.

Islands, Disease and Migration

Island ecosystems are more fragile than other terrestrial habitats. Island peoples have specialized in developing delicately balanced subsistence systems that allow extraction of necessary products without overburdening the resource base. Population pressure and natural disasters are potential problems for any human settlement dependent upon a limited resource base. On islands, however, there must be established mechanisms which alleviate extreme situations. One such mechanism is migration. It may be seen as a safety valve which opens and closes as needed. Today, migration also provides something different: access to new and exciting life-styles—the "city lights" syndrome.

Disease patterns on islands differ from those of continental land masses. The three major regions of

the Pacific vary considerably in their historical image with regard to health status. This variance influenced exploration, utilization of Islanders for labor and settlement by traders, missionaries and colonial administrative personnel. Melanesia was generally viewed as unhealthy for human habitation because there were "Plagues of insect pests and their attendant ills . . . and all manner of bacteria and parasites that deface the skin . . . and poison the blood."[1(p38)] Yet numerous tropical diseases are endemic throughout many islands in other parts of the Pacific—filariasis, malaria, dengue fever to name but a few. Communicable diseases are rarer on islands but more easily become epidemic once introduced.[8] Notwithstanding, Micronesia and Polynesia have generally had an idyllic image and this influenced the development of European settlement, tourism and ultimately the political status of particular island peoples.

The movement of populations, particularly on small islands, has an important impact upon disease patterns. There are many types of migration: It may be long-term, circular or permanent. Migration may be forced, voluntary or the result of disaster or population pressure. It may affect the health of those migrating, those left behind or those in the new environment. Transference of parasitic ailments from endemic areas to new environments, the spread of infectious disease, the possible amelioration of some health problems and inevitably the creation of new problems are all potential consequences of the migration of human populations.[9]

Pacific Island migrants to the US mainland do not bring with them the high incidence of infectious and parasitic diseases that characterize Southeast Asian immigrants. Rather, theirs tend to be the chronic diseases of civilization. Studies of Pacific Islander health and migration by teams of physicians, epidemiologists and anthropologists[10-17] suggest that the change from traditional small-scale subsistence life-styles to more urbanized Western living, whether in island urban centers or mainland Western cities, presents serious health risks.

Traditional island life-styles were disrupted by years of colonization. Diet, exercise patterns and social mechanisms for alleviation of stress have in some cases been transformed before migration from the home island. For instance, changes in type of food intake and food acquisition contribute to the currently high incidence of obesity among many Pacific Island populations. Processed foods such as cookies and crackers, breakfast cereals and soft drinks are becoming readily available and refined sugar, flour, rice and cooking oil are already staples in many Pacific Island households. Daily fish catches have been replaced by tins of foreign-produced mackerel, sardines or corned beef. Taro, cassava, banana and sweet potatoes, once daily staples, are planted in smaller amounts and often reserved for special occasions or feasts. The significance of the change is not just in the consumption of new dietary items but in the alteration of rigorous physical exercise patterns which necessarily accompanied daily subsistence activities. Pacific Islanders are eating different foods in different amounts and have become more sedentary.

Changes in socioeconomic status and assimilation to Western culture both take place during migration and are accompanied by behavior changes in food intake and acquisition. These factors increase the risk for the development of chronic disease among migrants. In fact, the process of migration itself may be a health risk.[4,10] In contemporary society, recent migrants are usually at the lower end of the socioeconomic scale, they have fewer skills than resident population groups and their world view and cultural expectations are based upon premises outside of the new host environment. They are under extreme social and economic pressures. The amount of change necessary to adapt to new surroundings and the resulting stress are without a doubt influential in potential health risks among immigrants.

The United States has become the largest recipient in the world of immigrants from other lands. However, immigration policy recently has changed and with it the most frequent type of immigrant. In 1968 the national origins quotas ended and the numbers of Asians and Hispanics increased.[18] As a result a new set of health problems among immigrant populations began to appear. Similarly new language and cultural problems arose. Pacific Islanders are categorized under the general heading Asian and Pacific Island immigrants, no doubt because they are both from the same general geographic region; yet, their political status, access to health care and disease patterns differ.

Pacific Islanders from American Samoa, Guam, Hawaii and the Trust Territories of the Pacific Islands are not refugees. They are quasi-citizens of the United States depending upon their individual political status. This varies according to US interests on each home island and local independence movements. They all have, however, free entry to the mainland and Hawaii. This is one reason that their enumeration is so difficult, but it is clear that their numbers are relatively small, especially when compared with Southeast Asian immigrants. Importantly, unlike other categories of immigrants, Pacific Islanders have access to state and federal subsidized health care.

Since Pacific Islanders are guaranteed access to health care one might ask why problems arise in provision of medical services to them. Two major factors seem to play a role. The first is related to cultural differences. Cultural and ethnic differences are among often neglected factors in medical care, particularly in the area of patient compliance. In the view of Western practitioners better health depends heavily upon changes in individual behavior; therefore, the individual person, rather than the state or the medical profession, is responsible for his or her own health status.[7] Pacific Islanders, however, do not always share the cultural

assumptions underlying this Western view and thus may not accept individual responsibility for health care needs.

Second, there are socioeconomic barriers to medical care for Island peoples. Provision of adequate health services to marginal peoples generally continues to be a problem of major concern to planners and providers. Poor people and welfare recipients in the United States do not receive the same quality of care as other classes within the population. Pacific Islanders are treated as second class citizens similar to Native Americans. Moreover, Islanders are displaced persons attempting to adapt to new social and ecological environments. Furthermore, their small numbers and ethnic diversity result in political factionalism and contribute to their invisibility in the polycultural health care setting, as well as in the society at large.

As I have stated above, individual ethnic identity is very important to Pacific Islanders, although, to outsiders, members of the various groups may appear similar. Their differences are important to them, and should be kept in mind by medical personnel providing them health services. In the following pages, I will discuss four separate groups: Samoans, Chamorros, Micronesian peoples and Native Hawaiians.

Samoans

Samoans represent the largest migrant Pacific Islander population in the United States. Most are American Samoan, although recently a sizable number of Western Samoans have entered via the American Samoa route. Estimated numbers of migrants vary, but from all sources it is clear that there are more Samoans living in Hawaii and the mainland than in American Samoa. In 1980 there was a population of about 32,000 in American Samoa; estimates of their numbers range from between 15,000 and 20,000 in Hawaii[14(p2)] and between 60,000 and 80,000 in California.[16(p508)]

Samoan early migration history to the United States has been well documented.[20,21] More recent observations suggest that in Hawaii, Samoan migrants are in the lower socioeconomic strata, have difficulties with English and lack work skills which would provide them access to the Hawaiian economy.[14] They live in neighborhoods near Honolulu and rural areas on Oahu. Current unemployment rates among young men in both Hawaii and the mainland reach 40% to 50%. Furthermore, there are few job training opportunities. In California, Samoans reside in large numbers in the metropolitan areas of San Diego, Los Angeles (Long Beach) and San Francisco (Daly City). The northern California community is socially and politically centered around 27 churches[16] and maintains a highly stratified political hierarchy and closed social network.

The major health problems among Samoan migrants are all diseases of modernization and are closely associated with obesity. These include cardiovascular disease, hypertension and diabetes mellitus (type II).[22,23] Generally, the migrant health status is not very different from that of modernized American Samoans on the home island. On Western Samoa, the average weight of men and women remains below US norms but in American Samoa, Hawaii[15] and California,[16] it is extreme by US standards. This is primarily the result of changes in food production, distribution and consumption. Also, migrants show significant elevations of blood pressure and blood lipid profiles.[22]

In many Polynesian areas aesthetic standards positively sanction fairly high body weights. These standards are giving way, however, among migrant groups. For example, obesity was identified as a sign of unhealthiness by 93% of a Samoan migrant sample population from eight Oahu communities.[37] Thus, changes in cultural perceptions regarding body type are taking place among the migrant group but not soon enough with regard to health risks for the first and second generations. This trend also seems to be taking place among the northern California Samoan population.

Mortality data for Samoan migrants are sparse; therefore, predictions of future health problems are difficult. Yet, it is crucial that state and federal health officials take notice of the trend toward chronic ailments among the Samoan migrant population. This is particularly important when considering the low socioeconomic status and high unemployment in the Samoan community.[14]

Within the health care setting, attention to health education should be emphasized with information regarding obesity, exercise and diet being promoted. A health educator/nutritionist working among Samoan adolescents in a California clinic has been successful when combining dietary education with competitive physical education programs in the public schools. A brief survey conducted at this same clinic suggests that compliance and patterns of use are highly influenced by culturally specific factors such as etiquette, morality and language use within the clinic.[24]

Chamorros

Guam and the Northern Marianas, separate political entities, are both part of the Mariana archipelago and share historical cultural heritage. Guam is an unincorporated territory of the United States and is a strategic military installation in the Western Pacific. The Northern Marianas which include Saipan, Tinian and Rota (the major population centers) at present make up a commonwealth in association with the United States. The major population group in both areas are the Chamorro, who came under colonial rule by Spain in 1565. Spanish language, religion and culture dominate the region even though the United States took possession of it after the Spanish-American War in 1898.

Guam has a population of 109,000, which includes 20,000 US military personnel and their dependents. About 62% of the Island population are Chamorro. The population of the Northern Marianas

is approximately 15,000 to 16,000 with more than three quarters being descendants of the original indigenous Chamorro peoples.[19(pp183,319)] The people of Rota, numbering about 1,500, have retained much of the traditional Chamorro life-style, primarily as a result of isolation.

Migration to Hawaii and the mainland United States is common and estimates indicate that at least 20,000 Chamorros live in California and at least 2,000 in Hawaii.[25] There are conflicting reports about any association between migration, westernization and the incidence of diabetes, obesity, hypertension, cardiovascular disease and malignant neoplasms among this group of Islanders.[26] However, there are extensive data concerning two fatal neurological disorders with high prevalence rates among Chamorro peoples from Guam and Rota.[27,28]

There exists in the Mariana Islands a high concentration of amyothrophic lateral sclerosis, locally called *letico,* and Parkinsonism-dementia, or *bodig.* Both disorders involve gradual paralysis of the entire body and are uniformly fatal. They are late-onset and account for almost one in five Guamanian deaths in persons 25 years or older.[25(p12)] Only the people of Guam and Rota within the Mariana Islands have these high incidence rates. Furthermore, these disorders develop in long-term Chamorro migrants to the US mainland also. The causes of both are unknown and there is no satisfactory explanation for the high frequency among the Chamorro peoples.

Micronesian Peoples

The Trust Territories of the Pacific Islands comprise more than 2,000 islands in three archipelagos: Marianas, Carolines and Marshalls. Present-day political subdivisions include the State of Palau, the State of Marshall Islands, the Federated States of Micronesia and the Northern Marianas. As previously pointed out, these Micronesian peoples vary extremely in phenotype, culture traits and language. They have "no common history until the end of the nineteenth century."[19(pp452-453)] Further differentiations have evolved as each group has had to adapt to different colonial rule. Spanish, German, Japanese and most recently American influences have been thrust upon these populations since Western exploration of the Pacific began in the 16th century. The total population of the entire political unit in 1980 was 136,000 and projected estimates are for an increase to 242,000 by the year 2000.[30(p44)] Family planning is a high priority among public health officials who promote building clinics and training personnel. But geographic isolation, small populations scattered around large expanses of ocean, lack of educated persons interested in remaining in the region and funding problems all combine to make health care problematic.

A large proportion of Palau's population resides on Koror, the government and commercial center where a district hospital is located. Population growth forces migration to Japan and the United States. Unlike other areas, the local cuisine, language and social behavior of the people has been heavily influenced by the Japanese occupation which lasted more than 20 years. The majority of Marshallese people live on Majuro Atoll.[19] Bikini Atoll became the site of nuclear testing by the United States. The original Marshallese inhabitants are under close medical observation and testing because of the health risks associated with radiation exposure.[31-33] The Federated States of Micronesia include Yap, Truk, Ponape and Kosrae. The government, trade, education and medical centers are small urban enclaves for the local populations from the scattered islands. These district centers absorb the rural to urban migrants. Some may go on to medical facilities, school or employment opportunities in Hawaii or the US mainland, but many remain in the town, unemployed and without land or sea rights and therefore unable to cultivate or fish for their food. Residents are overweight and dependent upon imported foods bought in stores and this leads to high frequencies of diabetes, hypertension and cardiovascular disease. Alcoholism and suicide, homicides, poisonings and traffic accidents are becoming more common.

Hawaiians

Native Hawaiians constitute approximately 19% of that state's population. In 1980 there were fewer than 10,000 full-Hawaiians—a people who in 1778 numbered at least 300,000[34(p41)]—while part-Hawaiians today number about 166,000.[35(p11)] They are a young population, with low personal income levels, rates of unemployment higher than any other group and proportionately higher rates of incarceration especially among juveniles. Life expectancy has always been lower than for other groups, and this trend continues today.[35] Full-Hawaiians are at the bottom of the heap in the multicultural Hawaiian social structure. Part-Hawaiians, however, have often assimilated to their non-Hawaiian heritage. Full Hawaiians on the other hand are like Native Americans on the mainland—people dispossessed on their own land.

Statistics having to do with health indicate a clear division between full-Hawaiians and part-Hawaiians. The full-Hawaiian population has higher rates of mortality from heart disease, cancer and accidents than part-Hawaiians or the "all-races" group.[35(p55)] Both full-Hawaiians and part-Hawaiians have high prevalence rates for respiratory conditions: asthma and bronchitis/emphysema. Infant mortality is high compared with other ethnic groups.

The factors contributing to the high death rates among full-Hawaiians are similar to what one might expect among a newly arrived migrant group to the United States. The Native Hawaiians Study Commission Report lists the following probable factors: income level; inadequate understanding of Western health care and a formal education; high content of salt in Hawaiian foods; cultural concepts of health and

illness that may affect self-diagnosis and willingness to seek treatment; genetic factors; the ability to resist diseases may be associated with ethnicity.[35(p56)]

A subject not covered in this paper has been the mental health status of Pacific Islanders. For both migrants and native peoples, such as Hawaiians, there are unique problems that result from the assimilation process. But for Native Hawaiians the main difference is that they have no choice but to remain in Hawaii. Some "perceive themselves as citizens of an unfairly defeated nation and some see themselves as an oppressed people."[35(p109)] The Hawaii State Department of Health admits that "the community's need for mental health services exceeds the available public and private resources."[35]

All Pacific Islanders are alike in their inability to return to an earlier way of living. Adaptation to the changing circumstances and environment cause strain on the individual organism. Some groups cope better than others. Islander identity helps to reduce the strain of assimilation and provides unity for the group. Mental health programs should be oriented toward culturally sensitive treatment and care in service delivery to targeted groups.

Health, Culture and Society

The diversity among Pacific Islanders is based upon fundamental biological differences, cultural adaptation to varied ecological settings, historical influences from a wide range of cultural forms and present-day political affiliations. What they share is an unfamiliarity with the urban US health care system, the stresses of migration, the isolation of separate language and culture and relatively low socioeconomic status.

There is little doubt that patterns of morbidity, mortality and health services closely follow along class lines. Pacific Islander migrants as well as Native Hawaiians enter the US social system at the lower end of the socioeconomic scale. They have higher rates of mortality yet underuse health care facilities, like many other economically or culturally marginal people. Support networks and guidance for utilization of health care services need to be established cooperatively by migrant community leaders, health care providers and government officials.[4] Bilingual staff should be available in clinics and particular attention paid to social categories such as gender, age and rank when treating Pacific Islander patients.

Without the cultural knowledge to interpret the medical system and its use, and lacking economic security or social mobility, Pacific Islanders are at the mercy of the existing government-subsidized health care facility and its health care workers. Oliver,[1] a Pacific historian, sums up the probable future for Pacific peoples:

> Interest and appropriated money will always be available for keeping the islanders healthy and educating them American-style. And pressure will be exerted continually to transform their mores and their social and political relations into American patterns. . . . [Pacific Islanders are caught between two worlds but one hopes] there remains the possibility that a people whose ancestors were so resourceful will be able to harmonize the cultural dissonances of the modern world into a new and equally satisfying kind of life for themselves. During the long centuries of Oceanic history they have done it before. Perhaps they will do it again.[1(p422)]

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Issues in Health Care of Middle Eastern Patients

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Relationships between Middle Eastern patients and Western health care professionals are often troubled by mutual misunderstanding of culturally influenced values and communication styles. Although Middle Easterners vary ethnically, they do share a core of common values and behavior that include the importance of affiliation and family, time and space orientations, interactional style and attitudes toward health and illness. Problems in providing health care involve obtaining adequate information, "demanding behavior" by a patient's family, conflicting beliefs about planning ahead and differing patterns of communicating grave diagnoses or "bad news." There are guidelines that will provide an understanding of the cultural characteristics of Middle Easterners and, therefore, will improve rather than impede their health care. A personal approach and continuity of care by the same health care professional help to bridge the gap between Middle Eastern cultures and Western medical culture. In addition, periodic use of cultural interpreters helps ameliorate the intensity of some cultural issues.

George Engel[1] has challenged Western medicine to broaden its biomedical model of disease to one that includes the psychosocial sphere—that is, to a biopsychosocial model—inasmuch as "the boundaries between health and disease, between well and sick, are far from clear, for they are diffused by cultural, social and psychological considerations." Such considerations are the focus of this paper, in which we discuss Middle Eastern immigrants and temporary residents who seek health care in the United States.

The number of Middle Easterners in the US has increased during the past decade as a result of continuing political instability in their home countries; consequently, the number who seek health care has also been increasing. Health care professionals, however, are still fairly unfamiliar with the unique cultural characteristics of Middle Easterners when they come for health care and are often apt to view them as "difficult" patients. The misunderstandings tend to be mutual. Although they respect American medicine in general, Middle Easterners, because of unmet expectations, may be confused and angered by health professionals.

Middle Easterners differ in their characteristics from country to country; most American health professionals, however, see them as similar. Disregarding for the moment the implications and political ramifications of generalizing about peoples as different as Egyptians, Yemenites and Iranians, there is an advantage in describing their shared values as well as offering suggestions that can guide health professionals in providing more culturally sensitive care. The observations of Middle Eastern patients and suggestions offered here are based on years of clinical work by one author (A.I.M.) and on current research involving Arab and Iranian immigrants by both authors. We will briefly discuss the effects of immigration on health in general and on that of Middle Easterners in particular.

Immigration and Health

In the process of migration, a family or a person loses a social network, the social, human resources on which they depend for both daily and long-term needs. An immigrant experiences a sense of disorganization and disorientation that manifests itself in a syndrome called cultural exhaustion or shock. Others' behavior and symbols no longer mean what they meant before migration and now require considerable energy to interpret. Attending to the basic needs of housing, obtaining

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food, learning the banking system and mastering English all require much energy. In addition, immigrants experience a degree of loss ranging from mild to most profound.

Published material on the subject suggests that migration causes immediate personal and social disorganization that slowly abates with time. The extent of individual difficulty depends on level of education, occupation, social status, formal social ties with the host country, personality traits, motivation for migration, whether migration is voluntary or involuntary, permanent or temporary and the magnitude of cultural differences between home and host countries—the greater the magnitude, the higher the potential for cultural exhaustion.

The relationship between migration and health is complex. Hull suggests that migration can affect life and health on every level:

> Migration affects health directly at the biological level via dietary changes, differences in local pathogens, lack of appropriate immunity, and through the risk of accidents in new situations. The social-psychological effects may affect health indirectly via the postulated physiological effects of stress and change on immunity to endogenous and exogenous infection, and by hastening system failure in chronic disease via a less well understood chain of events.[2(p34)]

Middle Easterners: Who Are They?

In contemporary usage, the Middle East encompasses a region spanning from Rabat (Morocco) to Tehran (Iran), a distance of roughly 3,400 miles[3] (Table 1). However, our observations reported here are based mainly on work with Palestinians, Egyptians, Jordanians, Yemenites, Lebanese, Iraqis and Iranians.

Arab-Americans are Arabic speaking people, usually of Semitic origin, who were born in an Arab country and migrated to the United States, or whose parents were born in an Arab country and who therefore consider themselves of Arabic origin. Armenians and Assyrians, who maintain their strong ethnic identification even when living in Arab countries and speaking Arabic, are not included in our concept of Arab-American. Arabs began migrating to the United States in 1875 and have continued in waves that have coincided with a number of political upheavals in the Middle East. Except for a small group of Yemenites who are farm workers, Arab-Americans are generally urban dwellers who work in industry and private business, including a sizable group of professionals or semiprofessionals in all fields.[4]

Iranian-Americans are of Indo-European origin and speak Farsi (Persian). Persian culture is very old, the Persian empire having been founded by Cyrus the Great in 559 BC. In the course of history, Iran absorbed numerous invasions, most notably the Arab conquest and subsequent Islamization in the seventh century, but always assimilated its foreign conquerors and maintained its cultural integrity.[5] Shi'ite Moslems represent about 90% of the population of Iran. In Arab countries, except Iraq, the majority are Sunni Moslems. The few Iranians who migrated to the US in earlier decades came here as students and decided to stay. The political turmoil since the 1979 revolution in Iran has been responsible for a recent large exodus of mainly middle- and upper-class Iranians to the United States.

The exact number of Middle Eastern immigrants and temporary residents currently residing in the United States is not known because of a lack of detailed census data, shifting US immigration quotas and political upheavals in the Middle East that bring many temporary residents, with and without visas, who are unlikely to be counted. Naff[4] estimates Arab-Americans to number slightly more than 1 million, 90% of whom are

TABLE 1.—*The Middle East**

Country	*Area Square Miles*	*Population*	*Major Language*	*Major Religion*
Arab Countries				
Algeria	919,591	17,422,000	Arabic, Berber	Islam
Bahrain	240	358,857	Arabic	Islam
Egypt	386,659	41,572,000	Arabic	Islam, Coptic Christianity
Iraq	172,476	12,767,000	Arabic, Kurdish	Islam
Jordan	35,000	2,152,273	Arabic	Islam
Kuwait	6,532	1,355,827	Arabic	Islam
Lebanon	4,015	3,161,000	Arabic, French	Christianity, Islam
Libya	679,358	2,856,000	Arabic, Berber	Islam
Morocco	172,414	20,242,000	Arabic, Berber, French	Islam, Judaism, Christianity
Oman	120,000	891,000	Arabic	Islam
People's Republic of Yemen	111,101	1,969,000	Arabic	Islam
Qatar	4,247	220,000	Arabic	Islam
Saudi Arabia	829,995	8,367,000	Arabic	Islam
Syria	71,498	8,979,000	Arabic, French, Kurdish, Armenian	Islam, Christianity
Tunisia	63,378	6,367,000	Arabic, French	Islam
United Arab Emirates	32,278	1,040,275	Arabic	Islam
Yemen Arab Republic	77,220	6,456,189	Arabic	Islam
Non-Arab Countries				
Iran	636,293	37,477,000	Persian, Azerbaijani	Islam
Israel	7,847	3,878,000	Kurdish, Hebrew, Arabic	Judaism, Islam, Christianity

*From Hammond Medallion World Atlas, Maplewood, NJ, Hammond Inc, 1982

Christian and 10% Moslem. Arab consulates estimate the number to be 2 to 3 million. Iranian-Americans numbered between 70,000 and 80,000 toward the end of the 1970s.[5] An Iranian newspaper article recently stated that there are currently about 200,000 Iranians in California, most of them living in Los Angeles.

Although in this report we describe general cultural themes, the readers should keep in mind the variations that exist between and within national groups of Middle Easterners. Country of origin, urban or rural origin and length of stay in the United States as well as religion are important aspects of these groups. Arab religions, in addition to Islam, include Christian sects like the Eastern-ritc churches, Coptics, Maronites, Melkites and Syrian and Chaldean Catholics.[4] Iranians may be Moslems, Zoroastrians, Chaldeans, Baha'is or Jews.[5]

Ethnic identity is another aspect to be considered. Individuals choose how strongly they identify with their ethnic group, regardless of degree of acculturation. Awareness of both ethnic identity and acculturation in a patient will give a health professional a more complete picture.[6] During the past decade Arab-Americans have emphasized their ethnicity increasingly since the arrival of new nationalistic immigrants.[4] Iranian ethnic consciousness has been heightened with the recent dramatic increase of immigrants from Iran.

Middle Easterners represent a wide socioeconomic spectrum in which level of education is the most important aspect. Some differences that observers note between Arab- and Iranian-Americans (such as, Arab-Americans are "more traditional and religious") more likely reflect differences in social class. Whereas Arab immigrants range from illiterate farm workers to well-educated or wealthy people, most Iranian immigrants are well-educated and upper middle or upper class and may be wealthy. They are typically more cosmopolitan than many Arabs. With these variations in mind, we will describe a core of shared Middle Eastern values and behaviors that may affect a person's relationship with health professionals.

Selected Cultural Themes

Affiliation and Family Style

To belong, to be affiliated with other persons, is a universal human need; the intensity of the need varies among individuals and cultural groups. The need for *affiliation* is dominant among Middle Easterners. They thrive on a large repertoire of relationships and family relations fulfill many affiliation needs.[7] During illness or crisis, Middle Easterners rely heavily on other persons instead of trying to cope by other means.

The extended family is the central, most durable and influential social institution of the Middle East.[8] Families gather and make spontaneous visits and intergenerational contact almost daily. Children live with their parents until they marry and maintain close contact with parents after marriage. When parents age, the roles are reversed. Children are expected to care for their parents as long as they live. The family structure is patriarchal; children are expected to submit to the father's authority.

Middle Easterners in the United States are often lonely; the extended family may be scattered or work schedules and pressures may not allow frequent and spontaneous visiting. They may feel isolated and complain about having to make appointments to get together.

The intense caring and involvement with family and close friends is accompanied by mistrust and doubt about the intentions of those outside the intimate circle. But the negative expectations can be rapidly reversed when someone moves from the stranger category to become an insider.[9] There are striking differences in the behavior toward, and the demands on, intimates versus outsiders.

Context, Time and Space

Context. Given the intensity and frequency of their relationships, Middle Easterners' culture is highly contextual—that is, persons seek understanding of events by examining the entire web of circumstances in which they occur. A Middle Easterner needs to know more about another person than an American does for a relationship to develop. American culture is low in context; the emphasis is on the verbal message and less so on the context in which the message is given.[10]

Time. Punctuality is less important in the Middle East than in the United States. A patient might be late for an appointment, or not come at all, because another matter immediately at hand was seen as more important than the previously scheduled appointment. Americans are annoyed by such a nonchalant approach to time, and the Middle Easterners may be offended by the American proclivity to immediately talk about the business at hand instead of taking the time to establish a relationship.

Space. The appropriate conversational distance between Middle Easterners is about .6 m (2 ft), in contrast to about 1.5 m (5 ft) for Americans. This proximity allows a Middle Easterner to finely read the other person's reactions in a conversation.[10] Middle Easterners touch more frequently. The American-born author (J.G.L.) needed months to become comfortable sitting shoulder to shoulder in a room full of Iranians and being embraced on greeting and taking leave.

Interactional Style

Studies of national character are considered to be of limited use; nevertheless, they have an intuitive appeal. Beeman[11] suggests that the regularity one feels in national character is due not to uniform character or emotions, but to uniform codes of communication that may hide a vast amount of individual, attitudinal, emotional and personality variation. According to Berger,[12] social history and personal development have combined to produce a society in the Middle East in which insecurity, hostility, suspicion and rivalry are compensated by strong adherence to religious ritual,

patterns of ingratiation and hospitality and a limited form of cooperation.

Westerners are often baffled by Middle Easterners' ritual courtesy toward strangers. Bateson and associates refer to "a constant flow of offers of hospitality, compliments, etc. which to the Westerner sound profoundly insincere, especially when he discovers that he has committed a social gaffe by taking them literally."[9(p270)] The social ritual presumes the restraint of the respondent, and allows a host the pleasure of saying "my house is your house" to a guest who knows when to go home. Ritual courtesy is practiced only between people of unequal status. Between intimates, requests are direct, material goods are common property and one person would "sacrifice himself" for the other.[11]

Middle Easterners desire to please or to appear good, and weaker persons must at all costs placate stronger.[8] Personal cleverness, so valued by Iranians, calls for thwarting direct interpretation of one's own actions, but for successfully interpreting the actions of others,[11] which is particularly apparent in "bargaining." In the "top man culture" of the Middle East,[10] the person at the top makes the decisions, and in Islamic society there are no intermediaries. The one with the most authority in any situation is usually the oldest and most educated person. Middle Easterners will attempt to obtain the services of the top person in a field, such as wanting to be seen by the head of a department in a well-known university medical center. Middle Easterners value social status more highly than do Americans; they are always interested in learning "Who is your family?" and "Who do you know of importance?"

Health and Illness Behavior

Middle Easterners generally have respect for Western medicine. However, in working with any immigrant population, health care professionals should keep in mind that folk beliefs and practices are often retained. Middle Easterners would not refute germ theory, but would place it side by side with other disease etiologies, such as the Evil Eye (*Ein el Hassoud* in Arabic, *Cheshmé Bad* in Farsi). They believe that a positive event, such as a promotion or giving birth to a beautiful baby, provokes jealousy and envy in others, giving the eyes of the envious party the power to inflict an accident, illness or other negative event on the fortunate person or family.[13,14] Some Arabs wear amulets with verses from the Koran or blue beads to encourage God's protection. Few Iranians would admit to a belief in the Evil Eye, but more than a few burn "esfand" (a kind of seed) because, as one Iranian commented, "The smoke is healthy, and it keeps the Evil Eye away. I don't know if there is one, but it won't hurt."

Food and other substances are believed to play a role in health and illness. Some Iranians use teas, such as *Gole gov zabon* (an herb) for nervous upsets or *Nabat* (a concentrated sugar) for stomach upsets. Iranians mention eating only fresh foods and avoiding canned or frozen foods to prevent illness. Humoral theory is evident among Middle Easterners in the use of "hot" and "cold" foods—honey and walnuts are "hot," cucumbers and yogurt are "cold"—and they avoid eating incompatible foods at the same meal. Inappropriate or inadequate diet is seen to cause weakness or illness.

Other causes of illness according to folk beliefs include exposure to cold and dampness, sudden fear, emotional upset and carelessness.[13-17] Illness is often associated with bad luck and poverty, health with good luck and wealth. A physically robust person is considered healthier than one who is thin. It is commonly believed that illness is sent from God as punishment for sins because God is seen to be afflicter as well as healer.[18] Health professionals have frequently observed among Middle Easterners a fatalistic acceptance of disease or death. Moslems are sustained in adversity by the belief that whatever happens to them is in accordance with God's master plan.[19] The Koran states that each person's fate is sealed from the moment their soul is created. Even though fate is predetermined, a person cannot know their fate, so it is wise to strive for God's favor through obedience.

Middle Easterners' pattern of somatization of anxiety or depression and their negative stance toward psychiatry is similar to that of Hispanics and Asians.[20,21] Ulcers and headaches are common among recently immigrated Iranians and are related to relocation stress and worry over the political situation in Iran. But Middle Easterners resist seeking help from psychiatrists because of the stigma associated with mental illness. Insanity is often attributed to evil spirits, head trauma, emotional trauma or sudden fright, but may also be attributed to heredity; families tend to conceal the fact that a member is a psychiatric patient for fear that their daughters' prospects for marriage will be jeopardized.[8] By the time psychiatric help is finally sought, a person may be very sick indeed. Middle Easterners are not adverse to seeking help for "nerves" and sometimes inappropriately consult neurologists.

Their expectations of encounters with physicians are culturally influenced. Preventive care is not practiced in the Middle East and medication is heavily used. Middle Eastern patients may complain that "The doctor didn't do anything," if they have not received a prescription. Injections are preferred over medicines in liquid or tablet form, colored pills are preferred over uncolored and larger over smaller ones.[8] But these preferences are more common among rural and less so among educated people.

Middle Easterners often fear hospital admission because hospitals are considered places of misfortune where people go to die. Moslems are concerned that a family cannot be sure that the body of one of its members will be treated correctly according to religious customs, should a patient die in hospital. These customs include bathing and clothing a body in prescribed ways and burying it in the earth, without embalming or

casket. Middle Eastern families often emphatically refuse an autopsy.[15]

Family Roles During Illness and Death

Discussion of illness and death of Middle Easterners of necessity focuses on the family. The affiliation needs of Middle Easterners are intensified during illness. A person seeking medical care may be accompanied by one or more persons who expect to be present during the examination or interview, who listen carefully and often answer for the patient. Usually it is an elderly person who will feel offended if not invited into the physician's office, or intimates of the patient who consider themselves duty bound to be there, lest their failure to be there is considered a lack of attention.[22]

The role of the family is to insist that a patient receive the best care possible from health personnel. Demanding behavior is prescribed by the culture and shows that the family cares about the patient. Family and friends are expected to show exorbitant concern, never to leave a patient alone and to constantly shower care and attention.

The family gathers when a family member is dying. According to Racy, "To die without issue or kin is the greatest defeat. To die surrounded by one's children and relatives is a great solace."[19(p874)] However, family members do not plan for death and never give up hope until a patient has actually died; grief is not permitted to be shown in the presence of a dying person. Once death has occurred, mourning is loud and obvious and expected to be so. Some women pound at their face and chest, others tear at hair and clothes; men sob openly. A person who is not overcome with emotion is not admired.[9] Condolences are the most binding social obligation; visits are expected not only from relatives and close friends, but from all acquaintances. Memorial services are held at the time of the funeral and several times afterwards, depending on the rituals followed by the family, such as first Thursday after death, on the 40th day and at the one year anniversary.

Health Care Issues

Several problems related to the cultural norms and values mentioned above were elicited through consultation requests we received from health professionals who work with Middle Eastern patients. The problems included difficulty in obtaining adequate information from patients, demanding behavior of patients' families, patients' disinclination to plan ahead and other communication obstacles.

Defining the Problem

Relevant information with which to understand a patient's presenting complaint is indeed difficult to get from Middle Easterners. Obvious problems with the English language are shown by a recent immigrant's statement that "A few hours before I go to doctor, I was thinking what I should say. I open dictionary to write the words, but the dictionary didn't have." Often Middle Easterners express vague symptoms, giving generalized and global descriptions of their health status. Vague physical symptoms substitute for anxiety or depression because Middle Easterners lack concepts that distinguish mental states from physical states, and their experience does not permit them to carefully describe signs and symptoms as they are associated with different parts of the body.

Passivity in the presence of a physician (an authority figure) also interferes with eliciting information. Because the authority of a physician is never questioned, a Middle Easterner is not likely to ask questions or give information that would contradict or "show disrespect." This very respect for a health professional's expertise prevents a Middle Easterner from understanding why a physician cannot diagnose and prescribe without resorting to tests and "irrelevant" questions.

A third obstacle to communication is the Middle Easterners' resistance to disclosing detailed personal information to strangers. Arabs value privacy and guard it vehemently, even though privacy within a family is virtually nonexistent. They view the comprehensive health assessment on admission with suspicion and as an intrusion until the relationship between medical problem and personal questions is made clear to them. A formal interview in a non-Arabic language tends to yield answers designed to please the interviewer, to save face and to absolve the family from responsibility for the illness.[23] Once trust with a caregiver is established, personal information is given more freely.

We remind readers that political refugees, such as Iranians, Palestinians and other Middle Easterners who are here illegally, are likely to be highly suspicious of the questions of any "official." They may assume that a health professional has direct and regular contact with the immigration office or other government officials.

Persistent and Demanding Behavior

Frequently a health care professional is confronted by an overbearing family and a seemingly docile patient. The family's indulgence of the relative and demands on the staff are intended to show their caring for the relative, but such behavior more often than not interferes with professional care. In the following example, the nursing staff of a neurology-neurosurgery unit requested expert consultation on a patient because "the nurses were burned out by the end of the day and asked not to be reassigned."

Mr Ali (as we will call him), a 69-year-old man who immigrated from Iran 12 years ago, was admitted for craniotomy and possible tumor. Even though he lived in another city, he was accompanied by his wife, three of his four adult children and the wife's sister. Mrs Ali remained at his bedside at all times, sleeping on a cot in the hospital room. Family members insisted that nursing staff take care of all activities of daily living and requested that no medical or nursing students be assigned to Mr Ali. Mrs Ali instructed the nursing staff on tasks whenever they entered the room. The nurses'

verbatim notes give a flavor of Mrs Ali's requests: "Quick, I need linen, where is linen? . . . I changed him. . . . He needs more pillows. . . . He needs to be washed. . . . I brushed his teeth, but after that orange juice, he needs them brushed and flossed again. . . . I have to go to dinner now; who will be with him when I am gone?"

A clinical nurse specialist, realizing that the wife, normally submissive to her husband, was behaving in a culturally appropriate manner during his illness, looked for additional cultural clues. A major issue was noted to be trust. The nurse specialist then visited the Alis daily and suggested that a nurse be assigned to Mr Ali for more than a day at a time. With this change, Mrs Ali's demands decreased considerably and Mr Ali became more cooperative.

Health professionals are likely to interpret a characteristic pattern of repetition in Middle Easterners' speech as condescending iterations. Repetition, however, is a style of communicating, not necessarily indicating that a health care provider has not heard. Repetition is used for emphasis and as an indication of the significance of the matter at hand. On the one hand, repetition is a characteristic of Moslem prayers, which may be repeated 110 times; on the other hand, Hall and Whyte[24] point out that the only way one Arab gets another to do anything is to "needle him."

The Perils of Planning

Planning ahead is a Western value, not a Middle Eastern one. There, planning may be seen as defying God's will and capable of bringing on the Evil Eye or some other misfortune. Medical or any preparation for birth or death is diametrically opposed to Middle Eastern values. These events should be left in God's hands until the moment when they occur. To "interfere" is to outguess God, an act that could bring disaster to a family.[25] For example, it is rare for an Arab mother to prepare clothing and a room for her infant before delivery. Similarly, resistance to birth control is related to a preference for spontaneity, trust in God's guidance and a suspicion that family planning potentially challenges God's will.[7]

Related to planning is the issue of compliance. Middle Easterners appear to comply with health regimens and professional advice, but in fact may ignore advice. This point is illustrated in the following example:

Another patient (we will call her Mrs Wahby) came to the outpatient department reporting vague complaints of fatigue and dizziness. A complete medical work-up revealed no organic causes for her dizzy spells. Her overweight prompted a careful taking of her nutritional history. Because her heaviest meal was the midday meal and because she shared this meal with her husband and sons who came home for it daily, she was advised to remove herself physically from the house while her husband and sons were eating. In addition, it was suggested that perhaps she should not prepare lunch at all and have members of the family who came home for the meal take it elsewhere or prepare it themselves.

Mrs Wahby seemed agreeable to the suggestion but also had profound misgivings. The midday meal is the main meal in Arab families and continues to be so in the United States. Furthermore, one of the most significant aspects of the motherly and wifely role is the preparation of elaborate meals. To advise Mrs Wahby not to prepare such meals and, even worse, to disappear from the house altogether, is inappropriate and incongruent with Arab culture, and impossible to implement. Mrs Wahby seemed to accept the advice given her because most Arabs believe that disagreeing with authoritative advice shows disrespect or at least a questioning attitude toward an expert. To discuss a prescription or question advice is not usual practice. Moreover, agreeing to heed personally unacceptable advice can be a face-saving mechanism that hides a sense of powerlessness in making the suggested changes.

Communicating Grave Diagnoses

Middle Easterners, although valuing open communication and truth in general, do not communicate openly in crises, disaster, grave illness and impending death. Middle Easterners' "denial" in such matters clashes with Western medical need for full disclosure of fateful information and causes ethical dilemmas for a health professional. Middle Easterners believe that because only God knows how poor a prognosis is, hope should never wane and to give up hope would mean to forfeit God's help. Hope helps a patient cope with illness, even if such hope is futile by Western standards. Confronting a patient with a grave diagnosis "is not only a tactless act, but an unforgivable one."[25]

A patient's family acts as clearinghouse for information and often intervenes forcibly to block communication about a grave illness. The family feels that nothing but harm could come from upsetting the patient, as, indeed, patients who are told about their malignancy often give up. Some form of nonverbal communication regarding the prognosis likely takes place, but verbal utterances denoting a fatal outcome are strenuously avoided. To speak of death is "to bring it about."[9]

Guidelines for Health Care Professionals

Our suggestions are based on the premise that quality health care includes respect for the cultural values of patients and that it is a health professional's responsibility to maintain a flexible approach to accommodate patients from varying backgrounds. We hope that health professionals will recognize the cultural characteristics of Middle Easterners to improve rather than to impede their care.

Information Disclosure

In reference to important medical information, health professionals should include a family spokesperson rather than communicate solely with a patient. The spokesperson is usually the oldest man present, because older men are considered to be wiser and more

able to cope with bad news with fatalistic reasoning. In some instances, the spokesperson may be a grandmother, though even she should be protected because women are believed to be more deleteriously affected by bad news. In the case of Mr Ali, the patient himself did not ask about his prognosis; Mrs Ali was consulted about hospital care and discharge planning and the oldest son was given the results of the pathology report.

A health professional must be particularly careful about how negative information is presented. A common communication practice in the Middle East is to reveal the news of a tragedy or a poor prognosis in stages. For example, a colleague learned that her mother in Egypt was ill. The colleague prepared to visit but was unable to get concrete information from her family. At each of several stops on her journey home, she was given slightly more information over the telephone: "She will recover. . . . She is in the hospital. . . . She has cancer." Not until the family was bringing her home from the airport was she told that her mother had died. Potentially upsetting information should be given gradually, within the context of other information and events, and carefully modulated with hope. Hall and Whyte[24] suggest that we should learn to control our so-called frankness in dealing with people of a culture that puts a high value on maintaining pleasant surface relations.

Once a grave diagnosis or poor prognosis is communicated, it should not be discussed again. A health professional should be sensitive to the customary ways of handling such information, namely, by using the family's choice of euphemisms. If death is anticipated, it is important not to suggest nor request a visit from a religious official until a spokesperson of the family clearly requests such a visit. To suggest or request a visit on behalf of the family violates the value of hope, "interferes in God's plans" and conveys an image of a health care system that "gave up." All that predisposes a mistrustful relationship between a patient and health professionals.

The Personal Approach

Many difficulties with Middle Eastern patients dissolve when a health professional is accepted into the family system. An approach that combines expertise and authority with personal warmth more likely encourages trust than would a stiff professional facade. Gaining initial trust may not be totally under a health professional's control. A young female physician may not be accorded the same respect automatically accorded an older male physician until she has proved her competence and patient and family get to know her well.

In the contextual culture of Middle Easterners, individuals are seen as members of families, groups and even universities; they will naturally be more comfortable with a health professional about whom they know something beyond the specialty. It is useful to offer some personal information in the interest of gaining trust and, if asked personal questions, one should not refuse to answer them. Withholding information may prompt patient and family to withhold important health state information. Volunteering personal information helps enhance a trusting relationship.

Because immigrants value courtesy and hospitality, a health care professional is well advised to take a few minutes to "warm up" before delving into the business of the appointment or visit. Similarly, food is heavily laden with meaning in the Middle East. Offering or receiving food is a powerful symbolic gesture of acceptance of a person. The Arabic saying "We ate bread and salt together" signifies social obligation to an insider. *Namek geer* in Farsi means "I have tasted your food, now I am your slave." One would not hurt someone with whom one eats. A nurse was not completely accepted by an Arab family until she accepted an invitation to a meal at their house. Accepting a piece of baklava or a chocolate helps provide the warm-up period before a health professional takes a history. However, if one is offered food, it is considered polite to initially refuse (so as not to appear too eager) but to accept when pressed. A firm and final refusal could be interpreted as a rebuff. Whenever possible, offering a Middle Eastern patient tea does much to give an initial visit a positive beginning.

Continuity of Care

Because health professionals give of themselves not only technically but personally, it will be helpful to sustain continuity of contact. Trust grows with cumulative experience; Middle Eastern patients and their families will become increasingly cooperative with increased contact and trust. As we have seen, Mrs Ali reduced her demands on nursing staff soon after the clinical specialist spent time with her and her family each day. In another case, Hisham was a child with leukemia who was seen by a number of attending physicians in a university hospital. Having the same pediatrician during the long hospital stay was the single most important factor in reducing the mistrust, bargaining, demanding behavior and frustration experienced by Hisham's family.

The increased effectiveness of just one person who is the main source of health care for a Middle Eastern family, however, engenders disadvantages. Intense contact can be emotionally draining and exhausting. Middle Eastern patients are likely to telephone their primary physician or nurse at any hour, day or night. They tend to involve a health professional in an ever-widening sphere of life events: One might be invited to a wedding, pressed for legal advice or consulted about any concern they consider appropriate for someone who has been taken into the family system. Health professionals sometimes hesitate to treat Middle Easterners because of the intense involvement. One should be aware that consultation time required by one Middle Eastern family is longer than for patients of other nationalities, and that scheduling should be arranged accordingly. It is useful to collaborate with the other

health workers involved with a particular family by conducting patient care conferences.

Mobilizing a Social Network

Middle Eastern patients who have few family members or friends in the area are unable to mobilize their own social network. Being alone when ill can be most traumatizing and so distressing as to interfere with healing. A health professional might contact a patient's acquaintances in the area, Arab social clubs or the consulate, if necessary. It is useful to recruit Arabic- or Farsi-speaking health personnel to visit a patient periodically; the difference in a patient's morale can be dramatic.

Use of Cultural Interpreters

Health professionals are well advised to use consultants as cultural negotiators to help resolve difficulties in caring for immigrant patients. Such consultants need not be health workers, but should either be bicultural or have in-depth experience with the population. Weidman's[26] term "culture broker" acknowledges the role of establishing links between separate cultures or subcultures. A culture broker interprets differences in language or communication style, value preferences and life-style to patients and health care professionals.

Cultural negotiators are provided by the Mideast SIHA (Study of Immigrant Health and Adjustment) project of the University of California, San Francisco. SIHA was developed in response to the problems confronting Western health care professionals and Middle Easterners who must negotiate their way through the American health care system. The SIHA project staff also conducts research on illness behavior, health risks and needs and adjustment patterns of Middle Easterners. Health professionals and institutions that serve multiethnic and immigrant populations may benefit from developing similar resources. Cultural interpreters can significantly improve health care for immigrant and ethnic patients.

Conclusion

The issues and problems in health care for Middle Eastern immigrants and temporary residents we have described are derived primarily from clinical and consultation experience. Preliminary research, however, supports these themes. Despite the difficulties in working with Middle Eastern patients, there are definite rewards. Once their trust has been gained, Middle Easterners show a strong faith in their practitioners and are very cooperative. Because they are emotionally expressive, the health professional gets immediate feedback, including the gratification of being intensely appreciated and of knowing where one stands. Once accepted into an extended family, the love, care and involvement one experiences can have a significant impact. A pediatrician who worked closely with an Arab family whose child eventually died of leukemia was so profoundly affected by the experience that, according to his statement, he felt he would never be the same. Working with Middle Easterners gives health professionals the enriching opportunity to experience another culture and the significance of close extended family and relationships. For most, the rewards more than balance the difficulties.

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Psychiatry and Chinese Culture

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When we examine the cultural characteristics that influence mental disorders and related behavior among the Chinese, no major differences are found between Chinese and other groups in the range of disorders or in overall prevalence. Several cultural factors influence the recognition and treatment of mental illness, among which are attitudes toward emotional display, somatic as opposed to psychogenic disorders and features of the traditional medical belief system in Chinese culture. The Chinese have a relatively favorable prognosis of schizophrenia, low rates of depressive illness, a strong tendency towards somatization and the presence of several unique culture-bound syndromes. From studying Chinese in Vancouver, it was found that they have a characteristic way of dealing with mental illness in the family, in that there is first a protracted period of intrafamilial coping with serious psychiatric illness, followed by recourse to friends, elders and neighbors in the community; third, consultation with traditional specialists, religious healers or general physicians; fourth, outpatient or inpatient treatment from specialists, and, finally, a process of rejection and scapegoating of the patient. The efficacy of Western psychiatric treatment of Chinese patients has yet to be objectively assessed.

From a growing body of accumulated scientific observations, especially in the past three decades, certain differences are becoming apparent in the ways Chinese patients manifest the symptoms and course of mental disorders and in which the family and society treat and cope with mentally ill persons. This has led to such important questions as the relative vulnerability and tolerance of the Chinese to specific stresses and the extent to which Chinese culture with its traditional health beliefs and practices influences the perception and management of mental illness and mental health-related behavior.

In examining the role Chinese culture plays in shaping psychiatry and mental health services, I have attempted to address four questions:

- Are there psychiatric phenomena peculiar to the Chinese?
- Are there psychiatric treatment modalities that are unique to the Chinese?
- Have the Chinese with their sociocultural traditions developed unique coping skills which have expressed themselves in a pattern of help-seeking and delivery of mental health services?
- Do the Chinese have a system of psychiatric knowledge or theory peculiar to Chinese culture, especially regarding causation, manifestation and evolution of mental illness and its intervention?

Characteristic Features of Mental Disorders Among the Chinese

There exist basic similarities in the psychopathology of mental disorders between the Chinese and the people of Western and other cultures. Two major similarities have been variously reported in the past and substantiated by the International Pilot Studies of Schizophrenia of the World Health Organization (WHO) and other international collaborative studies.[1,2] The first important feature is that the entire range of psychopathology observed in the West and in other cultures in terms of symptoms or syndromes have been observed in the Chinese. Second, all types of mental disorders including their subtypes, as described in Western literature, have been identified among the Chinese when standard Western diagnostic criteria are applied.

The overall prevalence rates of mental disorders and the rates for psychoses among the Chinese have been reported as roughly similar to, or at the lower end of,

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the reported rates of those from other cultures.[3] Such observations, however, cannot be yet regarded as conclusive or meaningful. Because epidemiologic studies that have been carried out in Chinese and other cultures up to the present vary significantly in their scope, methods of case finding, diagnostic criteria, sociodemographic measurements and data analysis, they have yielded no data for meaningful comparisons, especially where the overall rates of mental disorders are concerned.

Major Psychoses

Observations on certain specific types of mental disorders are amenable for comparison with other studies by virtue of the use of better defined diagnostic criteria.

Schizophrenia. The prevalence rates of schizophrenia in various studies range from 1.1 to 4.0 per 1,000, which are in the lower range of rates reported from other cultures.[3-6] It should be noted, however, that the above findings require further confirmation through systematic epidemiologic studies using standardized research methodology and well-defined criteria.

Two significant features among Chinese who have schizophrenia seem to stand out from the reported findings. First, a large percentage of schizophrenic patients in Taiwan are diagnosed as paranoid both in clinical and systematic comparative studies.[2-7] Second, the data obtained from Taiwan and Hong Kong seem to indicate a considerably favorable prognosis for schizophrenic Chinese. The Chinese schizophrenic patients in WHO's pilot study showed better prognoses than those from Western countries after two years and five years.[1] In Hong Kong two thirds of schizophrenic patients were found to have a lasting remission or showed only mild deterioration at a ten-year follow-up.[8] The hospital statistics I obtained during my visits in 1981 and 1982 also suggested a benign prognosis for schizophrenic patients in China.

In addition, to investigate the role biogenetic factors might possibly have in the favorable outcome of schizophrenia, the contribution of psychosocial factors peculiar to Chinese culture should be explored. It is conceivable that the strong supportive network traditionally embodied in Chinese families and the community may play a key role. It is also possible that the preindustrial Chinese societal structure, with its well-defined roles and functions for each person, might place fewer demands on sick persons and thus make it easier for them to regain their prescribed roles and functions.

Affective psychoses. Prevalence rates of affective psychoses in Taiwan and Hong Kong are lower than generally assumed rates in other cultures.[4,5,9,10] Manic disorders are in the majority in most studies. Whether this finding is due to underreporting of cases of depression or to overreporting of cases of mania because of differing cultural tolerance of the Chinese to the psychopathology of mania rather than depression deserves further study.

Senile psychoses. In sharp contrast to in the West, care for aged persons with senile psychoses has not been a major problem for families, society or psychiatric institutions in Chinese society. The prevalence rates of senile psychoses in a Taiwan survey[4] and rates of patients older than 60 years admitted to hospital with psychosis in Hong Kong[9] are relatively low. These findings should not be taken to indicate that senile dementia does not develop in Chinese or that they do not suffer from senile psychoses. The age-specific rates of senile dementia and psychoses in the Taiwan study are found to be comparable with those reported from Bavaria and Thuringia. It is conceivable that the low hospital admission rates of senile psychiatric patients reflect the protective attitude of the Chinese toward old people, sick or well. It is postulated that the Chinese community has a higher tolerance for old people, making them feel loved, wanted, respected and useful, which gives them a sense of self-respect and belonging. How much such traditional attitudes help retard the aging process or influence onset and course of senile psychoses is a subject for future medicosocial inquiry.

Minor Mental Disorders and Culture-Bound Syndromes

In the case of minor mental disorders and culture-bound syndromes, three elements seem to predominate in most studies regardless of whether they are based on hospital statistics or community surveys: (1) the very low prevalence rates of depressive illness, especially neurotic depression, (2) the large number of patients diagnosed as "neurasthenic" and (3) the relatively few cases of obsessive-compulsive neurosis among Chinese.

Depressive illness. It is fair to state that depressive illnesses among the Chinese have so far received little attention largely due to their perceived low prevalence rates. Findings from hospitals and outpatient clinics in the People's Republic of China confirm the generally held view that depressive illnesses are rarely diagnosed. For example, less than 3% of outpatient-clinic patients and about 1% of inpatients are diagnosed as having depression.

Several reasons have been suggested to account for the rarity of reported cases of depressive illness among the Chinese:

(1) The characteristics of depression, consisting mainly of dysphoric mood change, self-depreciation and guilt feelings, do not fit in with the traditional concept of "madness" in Chinese society, which emphasizes outward antisocial or bizarre behavior as the pathognomonic features. Therefore, persons with dysphoric conditions neither seek psychiatric help nor get reported in epidemiologic surveys.

(2) A Chinese reluctance to express or discuss one's own feelings, especially to anyone outside of the family, may also play a part in inhibiting the expression of depression.[11]

(3) Somatization, a prevalent form of symptom manifestation in Chinese psychiatric patients, especially in the case of minor mental disorders, is felt to play an important role in influencing the diagnosis of depression.[3,12-14] The application of Western diagnostic criteria

of depression, which consists mainly of the presence of dysphoric symptoms, would leave out a large portion of depressed Chinese whose prevalent symptoms are predominantly somatic and vegetative.[15] The recent research findings in Changsha, Hunan, where 87 of 100 cases of neurasthenia were rediagnosed as depressive disorders further support the important role of somatization in depressive psychopathology among the Chinese.[16]

Indirect but potentially important supportive evidence of somatization can be found from linguistic studies. It has been pointed out that the Chinese words expressing the emotional state of dysphoric mood or depression are surprisingly limited compared with the richness of somatic expressions to denote other emotions.[17]

(4) One cannot overlook the real possibility that indeed the Chinese people suffer less depression. It is hypothesized that such pathogenetic conditions for depression as divorce, alcoholism and drug abuse are less prevalent in China, whereas mutual help through an extended family or neighborhood alliance is more readily available for those under stress in Chinese society. This hypothesis deserves a systematic inquiry.

Neurasthenia. My visits to the People's Republic of China have confirmed the many reports of visitors and Chinese psychiatrists that neurasthenia is by far the diagnosis most frequently made in psychiatric outpatients.[16,18,19] There was even a large scale nationwide campaign against neurasthenia in the late 1950s and 1960s.[20]

The term neurasthenia seems to be variously defined, and is often used as a synonym for neurosis or even for minor mental disorders that include neurotic depression, anxiety states, hypochondria and hysteria. The vague and idiosyncratic usage of the term makes it difficult to objectively analyze many of the psychiatric findings reported on this condition—whether the focus is its epidemiology, causation, treatment or clinical and social significance. Most Chinese psychiatrists seem to be of the view that there exists a group of patients suffering from a similar morbid condition of neurasthenia, probably of similar biologic or neurologic causation as originally reported by Beard[21] and Ballet.[22]

The whole issue of neurasthenia calls for an intensive systematic and comprehensive clinical, epidemiologic and laboratory investigation. This research should use standard diagnostic criteria for redefining several subcategories that are labeled neurasthenia.

Obsessive-compulsive neurosis. The rarity of cases of obsessive-compulsive neurosis among Chinese has been consistently reported by observers through epidemiologic surveys and clinical statistics.[4,23] I made similar observations during my visits to the People's Republic of China. Tseng[24] regarded the strong ties of persons with a domineering and perfectionistic mother —a characteristic Chinese feature—to be the cause of ten cases of obsessive-compulsive neurosis he studied. He did not explain, however, why there are so few cases of obsessive-compulsive neurosis to be reported among the Chinese, if indeed such mother-son ties are specific to Chinese and by implication commonly found.

Culture-bound syndromes. A number of syndromes such as *koro,* frigophobia and *shen-k'uei* occur almost exclusively among Chinese. *Koro,* characterized by panic that the penis will shrink into the abdomen and the person will die, occurs mostly among young men of low social class with minimal education in South China, Hong Kong and Taiwan.[25,26] An epidemic of *koro* was reported in Singapore in 1969.[27,28] Frigophobic patients suffer from excessive fear and intolerance of cold in terms of temperature and foods of "cold" (yin) nature.[29] *Shen-k'uei* is characterized by weakness, fatigability, insomnia, anxiety and hypochondria. It is believed to be caused by excessive masturbation, nocturnal emission or intercourse, so it is often called sexual neurasthenia.

All of these syndromes have an important characteristic in common, that of somatization of anxiety or fear. It should be noted that traditional Chinese medical beliefs rooted in yin-yang theory play an essential role in the manifestation, perception and interpretation of the above conditions. How much culture-specific treatment modalities have been applied to deal with these syndromes is not known, as no such reports are yet available.

Another reported culture-bound syndrome, *hsieh-ping,* is a form of possession and a trance state, often associated with guilt or fear over laxity in ancestor worship.[4,30,31] It may be regarded as religiously sanctioned behavior or a coping mechanism. Similar pathological possessions occur in other cultures,[32] but these are not related to ancestor worship as with the Chinese.

Alcoholism

Alcoholism has never been a social or a medical problem in Chinese society anywhere in its long history, which can be regarded as a most remarkable cultural distinction.[4,33-37] The rarity of cases of alcoholism among Chinese assumes more significance in view of the popular use of alcohol for medicinal, culinary, social and religious purposes that is ingrained in their everyday living.

Although the Chinese high sensitivity to ethyl alcohol, due to a constitutional peculiarity, may in part account for their resistance to consuming large amounts regularly,[38] the social control mechanism of traditional Chinese society seems to play a significant role in preventing alcohol abuse.[39,40] It is conceivable, therefore, that westernization of the life-style accompanied by social disorganization and family breakdown, as seen in segments of Chinese society in Hong Kong, Taiwan and certain North American locations, might contribute to increased alcohol consumption leading to alcoholism. Concerns to this effect have been expressed in Hong Kong[41,42] and Taiwan,[20] but no noticeable increase has been observed in a community survey carried out in Vancouver[40] or in the People's Republic of China.[6]

Treatment Modalities of Mental Disorders

Western psychiatric treatments, with the notable exception of psychotherapy, have been widely applied in China and, to a considerable extent, have been generally accepted by the Chinese people. It is premature, however, to conclude that Western psychiatric treatment modalities are effective with Chinese patients, as there are few evaluative studies using comparable standardized criteria and research techniques. Even the widespread use of psychotropic drugs, electroconvulsive treatment and insulin shock treatments has yet to be objectively assessed for their effectiveness with Chinese patients through careful clinical research, taking into consideration various biologic, psychologic and sociocultural factors.

Cross-cultural psychopharmacology is an important issue to consider. For example, in my clinical experience, Chinese manic patients seem to require smaller doses of lithium carbonate per body weight and a lower blood concentration. In Japan similar findings were obtained through a large-scale collaborative evaluative study.[43] The antipsychotic drugs like phenothiazine derivatives can be effective on Chinese patients at about half the dose required by their Western counterparts.

Psychotherapy

That "Western insight-oriented psychotherapy is not acceptable to the Chinese and their effectiveness is in doubt" has become almost a conviction.[44-46] The fact that professional psychotherapy is not legitimized or available for the general population in Taiwan, the People's Republic of China or Hong Kong corroborates this general notion.[31] Such a common notion merits scrutiny, however; psychotherapy is and should be a central focus of psychiatry in any culture, for it distinguishes psychiatry from all other medical specialties as both a scientific system and a healing art.

The conclusion that insight-oriented psychotherapy is not applicable to Chinese patients is a premature one in that insight-oriented psychotherapy has not been properly and sufficiently applied to Chinese patients by well-trained Chinese psychotherapists, and most of the available reports lack clear descriptions of the type and method of specific psychotherapy applied. The development of psychotherapy both in its theory and techniques in the past 60 to 70 years has been such that it includes literally hundreds of different psychologic interventions. It is almost meaningless, therefore, to state whether Western psychotherapy works or does not work. A proper assessment requires a clear description of patients, their problems and backgrounds, and the actual methods, psychotherapeutic orientation, frequency and duration of treatment, targets or goals of treatment and assessment of the results to understand the effectiveness of the psychotherapy rendered.

Given the above reservations, the fact remains that there exists a considerable resistance to insight-oriented psychotherapy on the part of both the Chinese people as patients or family members and the Chinese medical system. The following hypotheses have been advanced to explain this deep-seated resistance:

- Chinese philosophy emphasizes harmonious interpersonal relationships, interdependence and mutual moral obligation or loyalty for achieving a state of psychosocial homeostasis or peaceful coexistence with family and other fellow beings.[11] This seems to have conditioned Chinese persons to seek the cause of their stresses or adjustment difficulties in their relationships with others rather than to look inward.
- For the Chinese, emotion or sex belongs to a person's privacy, which is jealously guarded from anyone outside the immediate family circle. Chinese are taught to avoid at all cost talking to outsiders of one's own private life or of feelings and emotional life with family members.[11]
- The medical belief system in Chinese culture seems to act against the use of psychotherapy as a way of resolving conflict because of the former's emphasis on organic causation of mental illness and the tendency to somatization.[17]
- The reliance on verbal communication as the sole or major tool for psychotherapy may make it difficult for Chinese people to accept, for they by tradition or training rely a great deal on nonverbal communication or symbolic figurative expression in conveying their emotions.

Certain elements in psychotherapy may be used effectively in treating Chinese patients. For instance, it is conceivable that family therapy may be a preferred approach in restoring patients' interpersonal equilibrium with the significant people in their lives. An effective use of nonverbal communication including body language should be encouraged for inclusion in the treatment techniques in Chinese culture. It is conceivable that a psychotherapist might take a more direct approach in manipulating the physician-patient relationship, at least in its early stage, to make patients accept the therapist's treatment modality. Through experimental studies one could test the above-mentioned hypotheses, which would further refine psychotherapeutic techniques for Chinese patients.

Coping, Help-Seeking and Provision of Mental Health Services in Chinese Culture

One consistent finding in Chinese communities all over the world is that the family plays a key role in coping and help-seeking when a member becomes mentally sick. However, some changes are being observed in Hong Kong and other rapidly westernizing Chinese communities in which the family appears to be playing a lesser role in taking care of the sick.[42]

From our research in Vancouver, it was found that Chinese families have a specific coping pattern for dealing with a serious psychiatric illness in the family.[47-49] This pattern is characterized by five distinctive phases that as a rule follow a typical sequential order. Phase 1 is a protracted phase of exclusively intra-

familial coping, sometimes lasting from 10 to 20 years. Attempts are made by the family to influence the abnormal behavior of the sick member with every possible remedial means and resource within the family to its limit of tolerance. This is followed by phase 2 in which trusted outsiders like friends and elders of the community are asked to help the family cope with the problems of correcting the abnormal behavior of the sick member. Phase 3 is characterized by inviting outside helpers such as herbalists, physicians or religious healers to attempt to treat the psychotic person who is still kept inside the family.

Phase 4 occurs when the sick member is labeled a mentally ill person by a physician or a trusted outside agency with which the family consults. This labeling also implies that the family has reached the limit of its resources in dealing with the psychotic member. A specialist's help is sought first on an outpatient basis and later, in-hospital treatment may be accepted. When the hope for recovery of the sick person fades and the psychologic and financial burden of caring for a mentally ill family member becomes unbearable, the final phase of rejection and scapegoating, phase 5, sets in. The family gives up hope and is reconciled with its "fate" of having a mentally ill patient in its midst for the rest of the patient's life or who is kept in a far-away mental hospital so that the family no longer has to think about him or her. Certain events of life or persons and sometimes bad spirits or bad *feng-sui* ("geomancy") are blamed for the fate of their having to be landed with an unfortunate, ill-starred mentally ill member.

As regards minor mental disorders, the pattern of help-seeking differs greatly from that with major psychoses, resembling more the help-seeking behavior for physical disorders.[50] It commonly starts with self-medication, followed by consulting Western-style doctors, then to Chinese-style practitioners and finally to a Western-style hospital for physical diseases. The sequential order of the above help-seeking may vary in some cases depending on the availability of services and the educational or socioeconomic condition of the family. Seldom do they end up in psychiatric facilities, especially inpatient services. As a rule, traditional Chinese medical practitioners play a more prominent role in the neurotic cases involving sexual dysfunction like *shen-k'uei.*

Traditional Medicine and Mental Disorders

Traditional Chinese medicine has retained its theoretic frame of reference and medical beliefs into the modern age and is still exerting an important and pervading influence on the symptom formation of mental illness and mental health-related behavior of patients and their families.[51-54]

In Chinese medical thought,[16,55-57] psychosomatic integration characterizes the relationship between psychologic and physiologic functions. According to its theory each of the five major emotions has a corresponding internal organ: the site of happiness is the heart, anger the liver, worry the lung, fear the kidney and desire the spleen. The imbalance of emotions disturbs the functional balance of these organs and vice versa. The excess, incongruence or lack of harmony of emotions is regarded as pathogenic, and a high value is placed on moderation and inhibition of emotions or affective expression. Once the physiologic balance is disturbed due to psychologic imbalance, however, methods of treatment are sought in physiologic or medical intervention rather than psychologic. The training of body-mind together, like *tai-chi,* is more valued as a preventive means than as therapy to restore emotional imbalance.

Chinese traditional medicine seems, therefore, to have exerted an inhibiting effect on psychiatry to develop into an independent system of psychologic medicine as in the West. Indeed, psychiatry has been given throughout Chinese history a marginal place in the total medical system.

Nevertheless, one should not underestimate the significant influence of traditional medical beliefs peculiar to Chinese culture on the manifestation or treatment of mental disorders. For instance, the prominent role somatization plays in the psychopathology of mental disorders and in illness behavior, as discussed above, has its origin in traditional medical thought, which is deeply imbedded in the everyday life of the Chinese. It certainly influences the preferred modes of treatment. It also offers an effective defense against the shame and guilt associated with mental illness, for the psychologic burden of a sick person or the person's family is greatly relieved by somatization, which represents an acceptable explanatory model to all concerned. Although somatization is not exclusively confined to the Chinese people or culture alone, its intensity and pervasiveness are such that Chinese somatization has a unique quality.[15,58]

A plausible explanation for Chinese somatization lies in the cultural emphasis on a "situation-oriented" approach to life. In the Chinese view, a person is a relational being living and interacting in a massively complicated role system.[59] Chinese culture emphasizes harmonious personal relationships as the fundamental element in achieving psychosocial homeostasis.[11] To the Chinese mind, harmony, interdependence and loyalty are keys to survival, peace and happiness. The unique quality of Chinese somatization can thus be regarded as having two major cultural roots—traditional medical beliefs and a situation-related approach to life.

Finally, one should always keep in mind that Chinese culture varies in different communities and is constantly changing despite the commonly held notion of its stability, durability and continuity for more than 20 centuries. The fact remains that it is changing with time and place through contact with outside influences and through its own evolution and revolution. This factor of variation and change should be taken into consideration when one looks at certain observed facts or attempts to grasp the conceptual frame of reference of any observation.

Conclusion

It is evident from the above that the question, Is there a Chinese psychiatry? cannot be responded to with an affirmative reply at this stage of psychiatric development. There is a hope, however, that some of the gaps in psychiatric knowledge and theory might be filled and a more cohesive scientific system developed in the not-too-distant future, if the current lively psychiatric research in Chinese communities continues.

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Curanderismo and Latino Views of Disease and Curing

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Curanderismo *is a diverse folk healing system of Latin America. Eight major philosophical premises underlie a coherent curing world view of Latino patients: disease or illness may follow (1) strong emotional states (such as rage, fear, envy or mourning of painful loss) or (2) being out of balance or harmony with one's environment; (3) a patient is often the innocent victim of malevolent forces; (4) the soul may become separated from the body (loss of soul); (5) cure requires the participation of the entire family; (6) the natural world is not always distinguishable from the supernatural; (7) sickness often serves the social function, through increased attention and rallying of the family around a patient, of reestablishing a sense of belonging (resocialization), and (8) Latinos respond better to an open interaction with their healer. These nuclear ideas or attitudes about health, illness and care are culturally patterned and are both conscious and unconscious (implicit). Moreover, expectations of the nature of the patient-healer relationship have implications for medical practice in general and psychotherapy in particular.*

*Curanderismo** is a general term for a folk healing system that, while characteristic of Latin America as a whole, shows considerable regional diversity.[1-12] The system involves folk healers called *curanderos*. I will describe the nature of curanderismo, its major underlying philosophical premises, the characteristics and practices of healers and beliefs held by the system's participants about the causes of illness. Finally, I will refer to some of the social functions of contracting a folk illness in Latino cultures, touching whenever possible on specific "culture-bound syndromes" encountered most frequently in the clinical practice of psychotherapy and general medicine.[13-19]

Often overlooked is that culturally different patients such as Latinos who appear for outpatient or inpatient health services bring with them preconceived ideas and expectations about what constitutes illness, what kinds of treatment procedures are effective and correct and what kinds of health services are most compatible with their life-styles. Curanderismo is based on a set of values, underlying beliefs and premises—that is, relatively fixed but implicit, often unconscious, notions of disease causation and cure. Cultural values and beliefs are based on a well-differentiated world view and on lifelong interpersonal experiences with significant others in various ritual healing contexts, either domestic or religious.

Curanderismo is not just a ragtag collection of superstitions; rather, it involves a coherent world view of healing that has deep historical roots.[20-22] Failure to recognize its importance for some patients is one of the most commonly encountered obstacles to better treatment; here the consultative role of the medical anthropologist working closely with other health professionals is vital.

Although it is useful to provide a general overview of curanderismo as an "ideal" system, I want to emphasize that though it is extremely widespread, there is tremendous intraethnic diversification.[23-26] Wide patterns of variation that exist among Latino communities or groups can be of great importance in individual cases.

For a physician, a simple description of the institution of curanderismo in some hypothetic Latino community is important and necessary as an initial orientation, yet the essential clinical issues also relate to the

*The terms curanderismo and curandero(a) are italicized only when they first appear in this text.

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variability of its use. For example, what types of persons use folk healers (curanderos) and who is likely to define a health problem in terms of folk categories of illness? Under what circumstances is the folk system bypassed in favor of regular clinical treatment? Such questions are ones we have to ask about all folk healing systems, although obtaining specific information may at times involve medical anthropologists, psychologists or other health workers experienced in realistically appraising diversity in the community.

While a person's culture is never the only determinant of his or her behavior, it often is the most crucial ingredient in intercultural interactions, especially between patient and healer. For example, even such a simple thing as failing to shake a Latino patient's hand vigorously in an initial interview may convey the impression of a cold and distant attitude that will cost the physician a cooperative relationship.

What I have to say is not as comprehensive as it might be in terms of psychoanalytic and anthropologic theories. I will, however, share some thoughts, feelings and observations based on personal experiences with an eye to what is clinically useful to know.[27-29]

In the Southwest as a whole, or wherever large concentrations of Latinos reside in the United States, an epidemiologic paradox exists that is related to the reported incidence of mental illness among Latinos in the state of California. Poverty, migration experiences and acculturation stresses have been shown to pose special threats to mental health in many large-scale urban psychiatric studies. If we add to this their experiences of prejudice and discrimination, the Latino population might be expected to suffer a particularly high incidence of mental illness, especially major illness requiring in-hospital treatment. Paradoxically, Latinos are strikingly underrepresented as psychiatric patients in public outpatient and inpatient facilities throughout the West.[30,31] In one study, for example, Latinos have been shown to comprise only 3.3% of the resident population in California's state hospitals for the mentally ill.[32] The expected figure would be much more like 9% or 10%, since Latinos constitute at least 10% of the state's population—in all, well over 2 million. This is in stark contrast to the proportional representation of California blacks in public mental health facilities. It would take us too far afield to probe all the possible explanations for this paradox, such as the role of the family in insulating members from stress, or the relative visibility of psychiatric disorder in non-English-speaking groups. In addition to these and other factors, it is probable that curanderismo is a factor in this paradox, in that Latinos seek help from ethnic curers, the folk curanderos, who offer a source of diagnosis and treatment for psychopathology that never gets formally reported elsewhere. That assertion is undoubtedly true, although the extent to which it holds differs from state to state and from region to region. For example, some studies show that curanderos are much more important in Texas than in some areas of California.[12,24]

It is incorrect to assume that because curanderos exist and assume some degree of symbolic importance among Latino populations, there is no need for mental health services in the barrios. This could be used as a convenient political rationale for not providing needed services to Latinos. Absurd as this rationale is, some anthropologists have unwittingly supported it. Moreover, it has taken on the role of a self-fulfilling prophecy: Because culturally relevant services have not been provided in the barrios, it is probably true that Latinos never use them. On the contrary, well-designed studies show that when culturally relevant services are offered to Latinos, they use them in greater numbers than does the Anglo-American control group. There is no support for the myth that because the folk system exists, Latinos cannot or do not respond resourcefully to psychotherapy or other treatment modalities when they are culturally relevant.[33]

Curanderismo is syncretic, eclectic and holistic; it is a mixture of beliefs derived from Aztec, Spanish, spiritistic, spiritualistic, homeopathic and modern, "scientific" medicine. Just as it would be erroneous to assume that urban Western medicine is rational and scientific in all its aspects, so it is also clear that curanderismo contains many elements based on empirical observation and shares certain scientific concepts and procedures with Western medical practice.

With regard to perceptions and definitions of illness in Latino folk culture, if a minor, natural illness persists, one of three things happens. Home treatment will be tried first by calling in either a physician or a neighborhood *señora* (usually an older woman) or perhaps soliciting friendly advice from an older person in the community, a *persona mayor*. The sick person may then decide to go to a folk curer, thinking that the illness has been caused by saints as some form of punishment. He or she may be a victim of ghosts or witches or something supernatural, as opposed to something natural. It is not unusual for the family to then decide that a particular illness has both natural and supernatural causes requiring simultaneous treatment by a curandero and a physician. Many believe that only a curandero can cure certain types or aspects of illnesses and only physicians can cure others.

Illnesses are generally perceived as natural or unnatural in nature.[2,10,11] If a Latino finally goes to a curandero, the preference is to select one from within the family and, as a second choice, one outside the family. The family consists not only of the nuclear family, but also an extended grouping that includes the ritualized, *compadrazco* network of godparents and *compadres* that exist around various life passages such as baptism, confirmation, marriage and other sacraments of the Roman Catholic Church.[2]

I will now discuss the world view of Latino culture and its relationship to sickness, health and healing.

Premises of Latino Curing

Because curanderismo is a holistic system, people seek help from a curandero for physiological, psycholog-

ical and social maladjustments. A social diagnosis may be as important as a physical one. A psychological diagnosis may be emphasized, depending on the situation. There are eight philosophical premises, propositions or concepts that most influence medical beliefs and expectations among Latinos. These underlying propositions, whether conscious or not, provide predispositions to behave in predictable ways over time and, as presuppositions, they form a significant part of a culture's world view—that is, about the nature of reality and the construction of the universe. The following eight premises may not be confined to Latino cultures, but they are basic to an understanding of health behavior among its members.

- *The Mind and Body Are Inseparable*

In the Latino world view, the mind and the body are inseparable; there is no perceived dichotomy between emotional and somatic ills. This idea is a source of confusion in the wider Anglo-American culture where the dichotomy is taken as a given, a natural aspect of the human condition. But for Latinos, it is natural to present emotional problems in their somatic aspects. *Los nervios,* "the nerves," can be referred to, for example, with regard to almost any physical illness.[34] The idea of a psychosomatic illness, then, is the most natural thing in the world for most Latinos. One application of this world-view premise is in the folk syndrome, *bilis.*

One of the main causative factors in any kind of physical-emotional illness in Latino culture is the belief that illness is the result of having experienced some strong emotional state.[10,22,35,36] Because of rage *(rabia)* and retaliation fantasies associated with rage, one gets and suffers from *bilis.* In addition to destructive rage *(bilis),* three other common folk syndromes linked in Spanish to emotional experiences are natural awesome fright or *susto,*[37] *envidia,* the gnawing effects of feelings of strong envy,[21] and *tristeza,* separation and loss, unresolved natural mourning or sense of abandonment. For clinicians natural fright or fear, envy, rage and painful loss are experiences recognized by modern depth psychology to cause physical symptoms. Within the cultural construct, it clearly identifies that destructive impulses and upsetting emotional experiences can cause interpersonal and intrapsychic distress.

Bilis is considered a natural disease, caused by experiencing livid rage along with primitive "eye for an eye" revenge fantasies. It occurs when a person is badly frustrated or coolly treated by others. It can also have social connotations, in the sense that there are socially patterned stresses throughout life—systematically structured stresses on the lives of Latinos and all minority peoples—in addition to the universal developmental crises that all people face. These critical periods or points in the life cycle are when a person is most vulnerable to a folk illness such as *bilis.* In the sociologic sense, the cause of *bilis* can be traced to frustrations caused by the oppression and deprivation of poverty.

With *bilis* it is believed that bile pours into the bloodstream and the person "boils over," causing strange symptoms, some of which overlap with other syndromes, such as *los nervios* (anxiety). The most common symptoms of *bilis* are vomiting, diarrhea, headaches, dizziness, migraine headaches, nightmares, loss of appetite and the inability to urinate. These are very close to the psychophysiological disorders and some of the conversion reactions we encounter in everyday clinical practice. Like *susto, tristeza* and *envidia,* this folk syndrome is caused by an emotional upset, leading to what is believed to be an "imbalance of yellow bile."

The socially structured stresses on men and women may be somewhat different in that they precipitate *bilis* in men more often than in women, and *susto* in women more often than in men.[38] The choice of the syndrome may also be culturally patterned.

In addition to strong emotional states, three other factors are believed by Latinos to cause sickness. These are (1) lack of balance or harmony inside and outside a person, (2) dislocation of certain real or imaginary parts of the body *(empacho* or *caida de mollera,* for example) and (3) diseases of magical or of supernatural causation, such as punishment by a saint.

- *Balance and Harmony Are Important*

One of the central problems of life is balance or harmony—emotional, physical and social. In curanderismo harmony or balance in all of these areas is important for one's sense of well-being; imbalance may produce disease or illness. It is believed, for example, that one can have a derangement or an imbalance of "hot" and "cold" substances in the body, and the same holds true of human relations. These ideas about balance or the lack of it derive from Hippocratic theory and the notion of humors or qualities. In Spanish they are called *calidades.* These qualities or aspects of food, for example, are often an important part of the belief system that Latinos bring to the treatment setting. Added to very similar Aztec theories of disease and curing, these Hippocratic ideas were incorporated by Spanish priests. They were compatible with the Aztec concept of order by a balance of universal opposites, such as night and day, hot and cold, good and evil. What came from the Spanish in the 16th century are beliefs based on Graeco-Roman theories of humoral pathology that dominated medieval Europe,[21] that the human body contains four humors, or liquids: blood, phlegm, black bile and yellow bile. Each humor is characterized by qualities of heat or cold and moisture or dryness. Blood, for example, is considered to be hot and wet. In my experience, the wet and dry concepts are rare among curanderos in Mexico and Puerto Rico as well as in the United States.

The human body is healthy, the Latino view of curing asserts, when it maintains an exact equilibrium between these opposed qualities of hot and cold and moisture and dryness. An excessive amount or deficiency of one humoral quality results in illness. Medi-

cal treatment therefore attempts to restore a proper balance of humors and their qualities. For example, bleeding for fevers or bloodletting to get rid of excess blood is one clear, if unusual, example of how to deal with an imbalance of that sort. Poultices, herbs, cupping, emetics and diuretics are also used in attempts to balance the *calidades* of the body. Foods and medicines classified as hot are those prescribed for "cold" sicknesses and cold ones are prescribed for "hot" sicknesses in order to restore the proper balance.[20,21] One frequently encountered example of this is penicillin, considered to be hot. If a person has what he or she thinks is a hot disease, there may be some resistance to taking penicillin—though not in all cases nor with every Latino. The resistance will not usually be overtly expressed and may be minimal or a total rejection, but it is a common culturally patterned belief that penicillin is hot. Clearly the notions of Galen and Hippocrates are still alive and are a basic part of Latin-American folk medicine. Another example is *chiles,* which are obviously hot, and after eating them one is not supposed to go outside right away into the cold night air or suddenly into a draft, because that would cause an imbalance.

Patients in hospital often ask for *cilantro* (coriander greens, sometimes called Chinese parsley), believed to be a cold food.[39] Women who have just given birth to a child, which is a hot condition, will not want to eat pork, which they consider to be a hot food.[2] To make a patient more comfortable and life easier for everybody, including nurses and other hospital staff, it is helpful to understand these concepts. One woman just would not talk about it except to somebody who was sensitive to her cultural heritage and beliefs, or until she knew somebody would take them seriously. She wanted *cilantro* and did not want to eat pork, and she could have created an uneasy and conflictual situation, had the hospital not called for a "psychocultural consultation" from a medical anthropologist.

- *The Patient Is an Innocent Victim*

A third underlying assumption in Latino thought is that in general patients regard themselves or are regarded by others as innocent victims of malevolent forces in the environment. An ill person is not blamed for being ill. Rather, some sort of intrusion has taken place with a subsequent disruption of internal order by a combination of inside and outside forces, which must then be destroyed. This is sometimes spoken of as an "invasion" or an "attack." Witches may be to blame,[13] or the cause of illness may be virulent bacteria, sorcery, poverty, an evil spirit or an angry saint.[40]

A variation on this occurs when there is a breakdown of internal order within a person, due to that person's transgressions, requiring outside support from the gods or saints, curanderos or the family. In other words, illness is not always the result of intrusion or attack. In both cases a curandero can be used, and ideally a patient is surrounded by unconditional love, care and support as a consequence of this "no fault" assumption. Therefore the sick person is indulged by family and friends, allowed to regress, be passive and receive expected social support throughout the healing process.

- *The Body and Soul Are Separable*

The fourth premise has to do with the relationship of persons to the spirit world, an important question to ask of any traditional medical system. The underlying assumption in curanderismo is that the body and the soul are separable. This idea, by extension, results in belief in the possibility of soul loss, or the soul traveling in dreams.[40]

In Mexico the more indigenous the culture, the more the soul is believed to separate from the body, whereas in urban cosmopolitan areas, soul loss has lost its sacred quality and *susto* is equated more with experiencing natural fright, rather than separation of the soul from the body. In Mexico *susto* can involve separation of the soul, but in other cases the causes seem to be totally secular.

The combination of physical, social and emotional factors in disease causation has been mentioned. In this combination of three interdependent factors, how does one account for the spiritual? I would include spiritual under the emotional or psychological. I can only speak of psyche in terms of modern psychoanalysis; we really mean what people have called soul—not soul in the conventional, religious sense, but in the sense of psyche or self. Part of the self is felt to be lost. The concept of the loss of soul because of internal or external change can be seen in terms of what modern psychology calls depersonalization or derealization in a patient. The link between curanderismo and religion is strong. In a positive sense one may consider religious life to be a form of self-actualization. Of course spiritual or religious experiences can also be negative. To the extent that religion is positive and promotes healing, it has to do with ideas of the sacred versus the profane. Psychotherapy can be said to belong to the realm of the sacred. Normally I do not use the word sacred, but I think the psychoanalyst and the rudiments of the psychoanalytic training are not so different from the shaman in a shamanic culture.

The role of religion is important because a person in curanderismo is in a very general way conceptualized as a soul that happens to have a body, whereas in the more modern ideas of medicine and curing, a person is first of all a body that may or may not have a soul; the notion is believed to be irrelevant. One can speak of soul according to religious dogma, or psyche, or the unconscious, or some sense of connection with the universal cultural polarities of matter and spirit. The practical consideration is that a curandero may treat the soul and later (or not at all) the body. A curandero (or, the feminine form, curandera) may want to have tea and chat, as with friends, talking about the cure and thus dealing with the psyche—that is, the soul—first. This is in stark contrast to the efficiency and the material body orientation of the modern physician who

might (to use a stereotype) look at a whole person in terms of "a diseased liver"—that is, a fragmented part.

- *Cure Requires Family Participation*

A fifth premise is related to the responsibility for getting well. To some extent this always rests with the individual patient in relationship to the curandero, but it can also involve a kinship group. In other words, the locus of responsibility for cure resides with the entire family.[2,41,42] The extended family offers mutual obligations and culturally patterned roles that provide support and reassurance for a sick person. The extended family aids in the healing process because persons are able to use social, emotional and physical resources in times of stress. Family involvement may also pose problems, however. Given the nature of Latino culture, the choice of treatment or modality might be family therapy, but not always so; an experienced curandero knows when to separate a mother-in-law from a wife and husband for therapy. A modern psychotherapist might separate an adolescent child from the parents—that is, not see the entire family together—or see the entire family together once a week and then sporadically or once a week see the adolescent alone. An experienced curandero who is sensitive to an adolescent child's need to express independence and separateness might do the same thing.

The emphasis on the family that occurs in varying degrees in Latino communities reflects a value placed on interdependence versus independence. Ego autonomy and independence are also Latino positively valued attributes. Contrary to Anglo beliefs, the macho ideal is not that of an authoritarian, belligerent or insensitive man but, in a positive sense, an individualistic man with dignity who provides and cares for people with whom he is in close contact. At times Latino world view places a much greater value on interdependence than on independence.[14] This is true of many culturally diverse patients with whom health professionals work. It is important to see this value orientation as equally as valid as autonomy and not to misdiagnose it as passive dependency or unhealthy symbiosis with the family. All too often passivity and dependency are confused with interdependence.[43] When I treat young Anglo-American patients who come in with feelings of alienation and lack of contact with family or community, who is to say—if we are as culturally sensitive as anthropologists encourage us to be—that such an alienated state is better than interdependence? Is the suffering any less? We need to value interdependence, too.

- *The Interpenetration of the Natural and Supernatural Worlds*

The sixth underlying assumption is that the natural world is not clearly distinguishable from the supernatural.[44] This is closely related to the fourth premise, the separability of the soul from the body. Because of this belief, activities such as propitiation, prayers, attempts to coerce the gods and saints into granting requests, sacrifice, penance, miracles and vows can be part of curanderismo. Notions about interpenetration of natural and supernatural worlds are not always conscious, but they always to some extent underlie Latino thinking. Because of this world view, what is known as sympathetic magic, usually divided into two different kinds, can assume importance.[40]

The first kind of sympathetic magic is imitative, or homeopathic. The assumption underlying this belief in the way that humans can control the supernatural is that "like produces like." Imitative magic functions according to laws of similarity; an effect resembles its causes. The best example is the voodoo doll, in which an image is destroyed and the victim the image stands for dies.

Contagious magic differs from homeopathic-imitative in that it functions according to laws of contact more than laws of similarity. For example, harm done to something once closely associated with a person will continue to act on that person at a distance, even much later after physical contact has been severed. Hair, fingernails, clothes, teeth and anything else that has been in contact with someone then take on energy, power and importance for some patients. One belief that is very widespread is that if a girlfriend *(novia)* wants to keep her boyfriend *(novio),* she gets his fingernail clippings, grinds them up and puts them in her evening chocolate. She then has control over him in some magical way and is assured that he will stay around.

- *A Sick Person Needs to Be Resocialized*

Often a sick person, in the framework of curanderismo, is considered to be a "deviant" who has to be resocialized, especially in cases where acculturative stresses are great.[5,32]

Contracting a folk illness is often related to acculturation and having such a disorder may ultimately have a beneficial social function. It is believed that Anglos do not get folk illnesses such as *bilis* or *susto,* that they are immune to these ailments. Merely being afflicted with one of them and accepting the diagnosis or any of the treatment procedures means that there is a cultural identification with *la raza,* or with the parent culture. The treatment process can be a way to reintegrate a person back into the broader culture and to provide new significance or renew the sense of "belonging to" one's culture. Ties to the community are re-established and, by accepting the cure, there is a declaration of acceptance of the more conservative Latin-American world view.

When traditional values are weakening and need to be reclarified, the interpretation of illness is given in a way that resists cultural change, acculturation and socially structured stresses. Illness dramatizes to others the evil consequences of cultural change if value conflicts persist. Illness defends "the old ways," in that disease is often attributed to the demands of Anglo society, or the facets of American life uncongenial to a patient.[2]

• *The Healer Is Expected to Interact Openly*

The last and eighth underlying premise has to do with the personality of a healer. In an ideal culturally patterned sense, a healer is expected to be warm, friendly and personal. There is also some emphasis on his or her education and training, but more attention is paid to a healer's connection to the sacred.[6-9,23,24] This is often spoken of as their "gift" or "call" *(llamada).*

Successfully treating Latinos requires an open and personal approach. A healer is expected to shake hands at initial contact, to establish friendly rapport and to take an active part in communicating and interacting with a patient. Expectations, in other words, call for the active participation of both patient and healer, as person to person, not as subject to object. The pertinent world-view premise here could be stated as follows: For Latinos, health and healing call for an active participation in life, if not a sense of communion.

In Latino dreams, fiesta is a metaphor for this precept,[27,29] and a popular Mexican saying puts it well: *La vida es una fiesta pero hay que bailar*—"Life is a fiesta, but one has to dance." The fiesta is a communal high in the classic Durkheimian sense, and it also reflects a basic value orientation derived from the cental role of communion in Roman Catholicism, which Octavio Paz[45] and others have described. More than the English Protestant colonial powers, for example, the Spanish Catholics mixed and created a mestizo blend throughout Latin America. There is a high value placed on mixing, coming together, ritual fusion and communion. One may also think of bargaining in Latino cultures: whereas at a marketplace a tourist may wish for a fixed price and the quick or efficient end of a sale, the Latino seller may expect to enjoy a satisfying interpersonal bargaining process and the reciprocity intrinsic to transactions with the customer. This model has its analogies in therapeutic encounters.

It follows logically from the Latino emphasis on interdependence that family therapy or consultation may be indicated, and that a healer is expected to take an active role in an interpersonal life process fundamentally characterized by the concept of *personalismo.* According to Abad and co-workers, this concept refers to "the inclination of Latin people, in general, to relate to and trust persons, rather than institutions, and their dislike for formal impersonal structures and organizations."[46(p584)]

In recent years several attempts to include knowledge of curanderismo and to integrate actual curanderos in the overall treatment process have been successful.[47,48] Such attempts must often rely on the use of interpreters and all the problems inherent in this approach, especially where the translation of symbolic communication is a major hurdle.[49-51] Nevertheless, there is much to say for consultation with folk healers when indicated, and especially for the role of a medical anthropologist who, in a different sense, also acts as a cultural broker. Finally, consulting a curandero as part of an overall treatment plan at least offers one hope that dangerous and expensive quacks who exploit will be sorted out from sincere and knowledgeable healers who have much to contribute. Both modern medicine and curanderismo would then stand to be mutually enriched.

Relevance to Psychotherapeutic Process

Although I hope the foregoing discussion will be of value to physicians in various specialties, I would like to emphasize here its relevance for psychotherapists. What are some of the implications of these world-view expectations for the practice of psychotherapy? First, a Latino patient does not expect, nor relate naturally or well, to the extreme neutrality or passivity of the proverbial "blank screen" so often mistakenly associated with psychoanalysis. On the contrary, a psychotherapist is expected to be a participant observer, to use a concept from anthropology and from the rich contributions of Harry Stack Sullivan and his followers.[43] Here, the psychotherapist engages in reciprocity, interacting and communicating in a personal and humanizing way. What Jung[52] called "the dialectical relationship" between physician and patient has also been called "open systems theory." It is what Langs[53] has termed "the bipersonal field [of] therapeutic interaction," reflected in the recent attention of psychoanalysts of all schools to the usefulness of countertransference reactions or the countertransference neurosis, and to the central role of projective identification in psychotherapy as a basically dyadic feedback system.[54,55]

One closed system listening to another closed system and making interventions has not been a productive model with Latinos. In contrast, a therapist is challenged to feel as involved as the patient, so that as a result of psychotherapy two open systems interact and change in relation to each other, analogous to a chemical interaction.

The open systems model does not imply inappropriate self-disclosure, picking up on trivia or using the friendly bartender approach to problem-solving. It does not imply that analytic psychotherapists should educate Latino patients, give them instructions or tell them what they should do with their lives. Nor does it imply that we try to gratify repressed impulses. To interact openly and to use the countertransference creatively can in fact facilitate analytic processes when they are distinguished clearly from these other forms of (nonanalytic) intervention and counterresistances on the part of the therapist.

The open-systems approach highlights the feelings and fantasies about the relationship between the two people in the room and how they affect each other. Whatever fantasies, thoughts, memories and feelings are mutually evoked are attended to. This is what Erikson has called the actuality of the analytic hour.[56] It means that our presence in the room is experienced with strong feeling; that the actual frequency of our interpretations, clarifications and confrontations may increase, and that we painstakingly attempt to make understanding statements rather than ask questions. The open-systems approach can lead to more profound

interactional involvement. Our willingness to listen carefully, but also to react and interact openly, will not violate the culturally patterned expectations of the Latino curing world view.

The concept of respect *(respeto)* also implies decency, a common humanness that requires people to interact with each other on that level first in spite of age, sex, class and caste differences. In other words there can be social status differences in behavior, but one must first establish rapport and respect; in Latino culture all other social relationships and interactions are dependent on that foundation.

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Curanderismo in Taos County, New Mexico—A Possible Case of Anthropological Romanticism?

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Interviews with 25 Spanish-Americans of Taos County, New Mexico, indicate that time and acculturation have greatly eroded the belief in and practice of curanderismo, *the traditional folk medical system of the Southwest.* Curanderismo *in northern New Mexico today has moved from being a primary and important source of medical care to one used alternatively and very occasionally in cases of pediatric disorders, chronic illnesses and pain, and for those maladies still classified according to the traditional folk beliefs.*

Over-categorization is the commonest trick of the human mind. Given a thimbleful of facts we rush in to make generalizations as big as a tub.

GORDON ALLPORT, 1958[1]

Anthropologic treatment of Spanish- and Mexican-American* culture has recently come under powerful attack by Hispanic social scientists and professionals.[2] (See Romano O, "Minorities, history and the cultural mystique," *El Grito* 1967 Fall, pp 10-11; see also Gutierrez JA's review of R Coles' *Children of Crisis,* Vol 4, in *The Texas Observer,* May 26, 1978, pp 20-21.) Boulette, for example, has decried the grossly stereotypic, culturally determinist and overly psychologic interpretations characteristic of much anthropologic analysis of Chicano social life and institutions.[2] She singles out for particular criticism the anthropologic model of the Spanish-American family as "extraordinarily familistic, extended and patriarchal," and the exaggerated importance given to the dominant values of machismo, *dignidad* and fatalism, a pervasive religiosity, passivity and noncompetitiveness in Spanish-American culture. This interpretation has found its way into the psychiatric literature on ethnicity and family therapy, resulting in the presumption of an inherent pathology in Mexican-American family dynamics due to problems with individuation, overinvolvement and enmeshment and sex-role stereotypes.[3]

But where the anthropologic "teleologic-cultural-tribal-mystical" primitivist bias is most evident (for Boulette) is in the extensive ethnographic literature on *curanderismo,* the folk medical system of traditional Mexican- and Spanish-American communities. She cites the "poorly designed" and "anecdotal" early studies of Madsen (1964),[4] Kiev (1968),[5] Rubel (1966)[6] and Warner (1977)[7] that attributed to largely poor, rural, Mexican-American migrant workers widespread belief and participation in the folk alternative to biomedicine. And she contrasts Kiev's study[5] of a half-dozen *curanderos* (folk practitioners) and their emotionally disturbed clients in a barrio of San Antonio, Texas (from which Kiev unfortunately generalized to the whole subculture), to more recent large-scale surveys of health beliefs and practices among urban Mexican-Americans[8] that indicate that folk healing has all but disappeared. The controversy concerning the prevalence of belief in and use of a folk medical system among Mexican- and Spanish-Americans has intensified in recent years as the number of physicians and psychiatrists interested in social medicine, medical anthropology and culturally sensitive family therapy has increased[9,10] and professional societies promoting the integration of biomedical, anthropologic and psychologic concerns and insights have proliferated.

Of all the alternative medical systems in the United

*We use both terms in this paper to include those groups of people who claim descent from Mexico as well as those (especially in northern New Mexico) who claim descent directly from (colonial) Spain.

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States, perhaps none has been so extensively documented as Mexican-American *curanderismo,* studies of which span more than three decades and encompass geographically dispersed groups in Arizona, California, Colorado, New Mexico, Texas and the borderland counties on either side of Mexico and the United States (Table 1).[4-6,8,11-21] The gradual discovery of regional, class, educational and acculturational variations within both rural and urban Spanish-American populations of the West and Southwest has resulted in the exercise of much greater caution today than previously when generalizing about Spanish-American culture and, in particular, health beliefs and behavior. Yet, some cultural patterns appear stable across rural-urban and class lines, among these: the centrality and strength of the family (both nuclear and extended) and of fictive kinship (such as *compadrazco,* "godparenthood"); the maintenance (especially by women) of a religious over a secular world view and a historically justifiable mistrust and avoidance of Anglo authority, professionals and institutions. All three of these cultural tendencies contribute to the well-documented underuse of social, medical and psychiatric services by Mexican-Americans[20,21,23,25] and a high degree of noncompliance to medical advice and interventions.[12,21] And these same cultural tendencies contribute to the maintenance (albeit in different forms and varying degrees of pervasiveness and intensity) of an alternative medical system in *curanderismo.*

The Research Problem

In this paper we address the current debate on *curanderismo* by reporting on the extent to which a selected group of bilingual Spanish-Americans in rural Taos County, New Mexico, continue to support their traditional medical system, which was first described by Saunders in 1954[11] and which, to our knowledge, has not been restudied since. Rural Taos County offers a welcome contrast to the studies of Mexican-Americans especially in California and Texas where Chicanos most often represent a poor, migratory and economically exploited ethnic minority. The Spanish-Americans of northern New Mexico are in the majority and wield cultural and political dominance over both the *Indios* (Pueblo Indians) and Anglos (non-Hispanic whites). The population of Taos County in 1978 was 18,816, of which 15,505 were Spanish-American, 1,621 were Anglos and 1,300 were Native-American residents of the Taos pueblo. The Spanish-Americans of Taos refer to themselves proudly as *los primos* (the first colonists), and they claim family ties to the land extending back as far as the 16th century. There is a widespread cultural fiction that the Spanish-American population of northern New Mexico has *not* been periodically replenished by Mexican-American migrant workers, who are said to settle only in the southern half of the state. Except among the highly politicized youth of Taos, there is no strong sense of kinship or solidarity with the newer wave of Mexican immigrants, and older Taoseños disdain the terms "Chicano" and *La Raza,* which they feel do not express their own special heritage and history in the Southwest. In all, cultural dominance, rather than discrimination and forced isolation, has contributed to the maintenance of indigenous traditions and institutions in Taos.

Curanderismo: The Saunders Study

Between 1958 and 1963 Saunders directed a five-year study on the medical beliefs and practices of Spanish-Americans in northern New Mexico, centered in Taos County.[11,26] The resulting report gives the impression of the existence of a long and well-established tradition of popular medicine that has been periodically replenished from various sources: European, Anglo-American and Native American. Intrinsic to the system, however, was the elaborate and highly organized institutionalization of human-divine relations with regard to health and illness. God was viewed as the ultimate source of disease even as He was the ultimate wellspring of health and healing. A person accepted good health as a "gift of God," and sickness as an expression of the Divine Will. Chronic illness, which was part of one's fate *(destino)* was to be endured stoically and impassively; belief in *destino* was used to explain the low utilization of available health services by rural Spanish-Americans for conditions such

TABLE 1.—*Representative Studies of Spanish-American Medical Beliefs and Practices**

Study, Year	*Research Locale*	*Population/Social Class*	*Method*
Saunders, 1954[11]	Taos, NM	Rural/lower class	Ethnographic
Clark, 1959[12]	San Jose, Calif	Urban/lower class	Ethnographic
Holland, 1963[13]	Tucson, Ariz	Urban/lower and middle class	Survey
Madsen, 1964[4]	Texas	Rural/lower and middle class	Ethnographic
Rubel, 1966[6]	Texas	Rural/lower and middle class	Ethnographic
Martinez & Martin, 1966[14]	San Antonio, Tex	Urban/lower class	Survey
Kiev, 1968[5]	San Antonio, Tex	Urban/lower class	Clinical and ethnographic
Jaco, 1969[15]	Texas	Rural-urban/mixed class	Epidemiologic
Weaver, 1969[16]	Orange County, Calif	Urban/lower and middle class	Survey
Torrey, 1969[17]	Santa Clara County, Calif	Rural-urban/mixed class	Clinical
Edgerton, et al, 1970[8]	Los Angeles	Urban/mixed class	Survey
Kay, 1977[18]	Tucson, Ariz	Urban/lower class	Ethnographic
Schreiber & Philpott, 1978[19]	Texas border counties	Rural-urban/mixed class	Survey and ethnographic
Keefe, et al, 1979[20]	Santa Barbara, Calif	Urban/lower and middle class	Survey
Anderson, et al, 1982[21]	Corpus Christi, Tex, and border counties	Urban-rural/lower class	Clinical and ethnographic

*Adapted from Schreiber and Homiak.[22]

as a persistent, hacking cough, anemia and migraine headaches that by Anglo standards would require medical attention. A tendency to conceal illness, interpreted in men as a sign of weakness and lack of virility and in women as a sign of divine disfavor, also contributed to the characteristic stoicism. Saunders described Spanish-Americans as having little concern with health maintenance through basic preventive strategies such as well-care, periodic checkups, immunizations, special diets and the like due to a disabling present-time orientation and a belief that the future lay in God's hands. "Faith and fatalism," he concluded, "are the first ingredients in Spanish-American folk medicine."[11(p152)]

Spanish-Americans subscribed to an elaborate system of folk beliefs that broadly classified physical and mental illnesses as "natural," "magical" or "psychologic" (interpersonal) in origin. Saunders attributed widespread popular belief in the following eight major folk ailments:

Natural

1. *Aigre* or *mal aire* ("bad air"): nausea, vomiting, headaches, dizziness, earaches, facial paralysis or twitching of facial muscles caused by exposure to drafts and night air.
2. *Empacho* ("intestinal obstruction"): abdominal pain, constipation, loss of appetite or bloating caused by the adherence of food to the intestinal wall.
3. *Mollera caida* ("fallen fontanelle"): listlessness, colic, loss of appetite and an inability to suck in infants caused by the fontanelle caving in on the soft palate.

Magical

4. *Encono* ("festering of wounds"): infection of an open wound or of a surgical scar by exposure to a person (called *enconadores*) who unintentionally or, less often, intentionally causes the wound to fester.
5. *Mal ojo* ("evil eye"): a sudden reversal in the physical or emotional well-being of an infant or young child resulting from the admiration (implicitly, the jealousy) of a person with "strong eyes."
6. *Maleficio* ("witchcraft"): any inexplicable physical or emotional disorder caused by the malevolent magic of a *bruja* (witch).

Psychologic and Interpersonal

7. *Melarchico* ("melancholy"): depression, loss of appetite and insomnia caused by any change in the immediate environment, but especially by the loss of, or separation from, a loved one (especially a child from its mother).
8. *Susto* or *mal de espanto* ("fright," "shock"): general malaise, insomnia, irritability, depression, nightmares and wasting away caused by a fright or an emotional shock (especially the news of the death of a loved one).

According to Saunders, uniting these diverse beliefs was a single, larger explanatory model of health as equilibrium (as in the balance of "hot" and "cold" elements and in the regulation and monitoring of expressed emotion). The traditional belief system did not clearly distinguish mental from organic ailments and lacked the Cartesian dualism fundamental to biomedicine.

Response to Illness

Saunders's study indicated that when Spanish-Americans became ill they relied on self-treatment and on an extensive lay-referral system—advice from family members and neighbors—before seeking professional medical care (whether folk or cosmopolitan). Biomedicine was poorly understood and viewed as one among several competing resources from which to draw. Diseases were divided into those common ailments shared by all people (colds, flus, accidents and so forth) and those illnesses specific to Spanish-Americans (the "folk" illnesses) and, therefore, best treated by one of the four classes of folk healers: *curanderas* or *médicas*—persons with extensive knowledge of diagnosis and folk healing, *sobadoras*—specialists in therapeutic massage and bone-setting, *parteras*—local midwives who also treated a variety of female disorders and *albolarias*—persons who treated the victims of witchcraft. Most commonly, however, illnesses were treated at home with a wide variety of herbs that were collected in the wild, grown at home or bought at a pharmacy in town. If these traditional and home remedies failed, a relative or neighbor (usually a *señora,* a respected and knowledgeable older woman) might be consulted. Only after repeated failure in the private and domestic sector would a professional folk healer be used. The strategy of *last resort,* according to Saunders's original study, was cosmopolitan or biomedicine.

Research Questions, Methods and Interviewees

Our specific research objectives were to assess the degree to which Saunders's findings were representative of the norms of health and illness beliefs of contemporary *Taoseños* and, further, to what extent ethnomedical beliefs actually influenced patterns of health care seeking. Consequently, our research questions reflect some of the major topics of Saunders's study:

- Spanish-American definitions of health, illness and preventive medicine; perceptions of the stages of illness;
- the extent of local knowledge of and belief in the traditional etiologic and healing system;
- use of traditional home remedies and of folk practitioners, and
- use of physicians, clinics and hospitals; assessment of biomedical health care delivery in the Taos area.

Information on these questions was obtained during the summer of 1979 (with a brief return visit in the summer of 1983 by one of us [N.S.H.] to discuss aspects of this paper with representatives of the Taos community) through a standardized list of questions (Figure 1) followed by in-depth and open-ended interviews by the coauthors—both of whom are medical anthropologists—and two research assistants—one an anthropology graduate student, the other a social

worker and native-born Taoseño. In addition to the interviews, one of us (N.S.H.) also conducted observations in various clinical settings in Taos County: the hospital, private and public clinics, drug stores, churches and a healing shrine.

A total of 25 Spanish-Americans (20 women, 5 men) were interviewed in sessions lasting from a minimum of one hour to several repeated visits with the same key informant. The sample was an opportunistic one and whereas systematic sampling techniques were not used, there was an attempt to obtain heterogeneity of representation. Some of the respondents were contacted through casual encounters in the town plaza, library and pharmacy; others were reached with the helpful introductions of local priests, shopkeepers and bartenders, and two were relatives of our Taoseño assistant. In all, five rural hamlets plus the town of Taos were represented in the sample. The sex difference—that is, 20 women and 5 men—was partly the consequence of the greater availability of women for a rather time-consuming task during the day, but it was also intentional given the greater knowledge and responsibility of women in this culture with respect to the health and illness of family members, especially children. The respondents ranged in age from 16 to 79 and averaged 49 years. Seventeen of the respondents were currently married, four were widows, one was separated from her spouse and three were single; 22 of them had children. Fifteen were employed outside the home: four were professionals or paraprofessionals (a school teacher, a mental health worker, a social services worker and a licensed practical nurse); seven were employed in clerical, sales, service or domestic work, and four were laborers. They averaged nine years of education, although this ranged from 11 persons with less than eight years of school to three college graduates. All but three considered themselves Roman Catholics, and these three were fundamentalist Protestants. In all, 23 had been born in Taos County and, in most cases, claimed ancestry in northern New Mexico for several generations. All of the respondents were bilingual (though frequently fully literate only in English), with the exception of one elderly widow who spoke no English (at least with us).

Results

Definition of Maintenance of Health

Most respondents in our study defined health as feelings of mental and physical well-being and the ability to carry out normal role (and work) responsibilities. In this they differ little from Anglo norms. Rather than a passive or fatalistic attitude toward disease prevention, all but one of our respondents suggested a variety of behaviors or activities conducive to maintaining health, among these a diet rich in "natural" foods; relaxation techniques; adequate rest, and the avoidance of excess in all areas of life, including work, play, study, drinking and in emotions (especially envy, jealousy, fear and anger). Avoiding alcohol and tobacco ranked high on their list of illness prevention strategies, as did avoiding excessive work. Only with respect to the still-prevalent belief in the pathogenic nature of strong emotions did our sample conform to Saunders's description.

Classification and Cause of Illness

All the persons in our sample clearly differentiated *physical* from *mental* illness, just as they distinguished "scientific" or biomedical from "folk" ailments, which they referred to as Spanish illnesses or, among the skeptical, as "superstitions."

Illness was uniformly viewed as an undesirable state that was defined as an inability to carry out ordinary functions or to enjoy life. Weakness, pain, malaise or irritability, loss of appetite and fever were, in that order, the most frequently listed symptoms of ill health. The immediate responses of informants to questions regarding the causes of physical illness would be indistinguishable from the prevailing causal beliefs of Anglo-Americans in Taos, with emphasis on contagion, infection and accidents. Susceptibility to illness was related to a weak constitution, bad habits such as smoking and drinking, unnecessary exposure to the elements and poor dietary habits. Several informants noted that a "poor outlook on life" or a "bad mental state" could contribute to illness.

All but four of the respondents indicated that they knew of someone in their community who was mentally ill. While they entertained various theories of causality, the most frequently mentioned contributor to mental problems was family and interpersonal conflict. A third of the persons attributed mental illness to an innate weakness in either constitution (as in "feeblemindedness") or character (as in alcoholism, personality disorders or plain "craziness" or *locura*). Some persons, it was widely held, were simply unable to cope with normal difficulties or daily pressures. Among the younger respondents there was a tendency to attribute mental illness to the use of hallucinogens and other drugs, whereas among the older informants (in this case, five of them) the suggestion that a lack of faith in God and in His Divine Providence contributed to anxiety and depression. Only one elderly widow in the sample volunteered that witchcraft *(maleficio)* was behind some dramatic and violent cases of insanity. The Spanish-American mental health worker included in our sample, however, suggested that a belief in and fear of witchcraft, while not an uncommon "presenting symptom" among both Spanish-American and Pueblo Indian clients of the mental health clinic, was viewed generally by concerned family members and neighbors as disturbing and deviant behavior in a patient. There was broad agreement that mental problems constituted illnesses that were best treated by physicians. For severe or otherwise unmanageable cases of insanity, informants uniformly supported the placement of the patient in a mental hospital for custodial (protection of the community) as well as therapeutic reasons. None suggested pastoral counseling as

A. Demographic Information

NAME _____ ADDRESS _____

AGE _____ OCCUPATION _____

Spouse's Age/Occupation _____

Education (ego, spouse) _____

Years/generations resident in Taos _____

HOUSEHOLD CENSUS (relationships/ages of persons in household) _____

_____

B. Stages of Illness

1. How do you know that you are not well (what symptoms tell you that you are sick?)
2. Once you know you are not well what do you do?
   a. Do you seek advice from anyone first (spouse, relatives, neighbors?)
   b. Do you attempt to treat yourself first (how? any home remedies?)
   c. What kinds of symptoms concern you the most?
   d. In terms of loss of health, what is your greatest fear? (is there any particular kind of sickness, disability, affliction that you particularly fear?)
   e. How would you say you usually respond to pain?
3. How should a sick person behave? (stay in bed? try to work as much as possible? try to get around as much as possible?)

C. Illness Episodes

1. Has anyone in your family or household been sick over the past year? (who was sick, what was the illness, what did you do about it?) How about in the past few years? (same questions)

D. Utilization and Evaluation of Medical Care

1. In the past year how often has someone in the household seen a doctor, nurse, or other health professional? (explain circumstances)
2. On a scale of 1 to 3 (1 is best) how would you rate the medical attention you have gotten this year?
3. When looking for a doctor (or nurse) what are the qualities you think are important?
4. On what basis do you finally decide which doctor to use?
5. Do you have a family doctor? (how do you get to his clinic, office?)
6. Have you ever **not** seen a doctor when you thought that you or a family member should have? (why?)
7. Are there any people other than medical professionals that people in the community consult when they are ill? (who?)
8. After you see a doctor do you generally follow the prescribed treatment? (are there any kinds of treatment you particularly object to?)
9. When do you know that you no longer need to be under a doctor's care?

E. General Questions

1. What does being healthy mean to you?
2. What do you do to stay healthy?
3. What kinds of things are most harmful to people's health?
4. What does being sick mean to you?
5. Why does God allow sickness and suffering in the world?
6. What, in your own words, is the definition of a good life?
7. Do you have any views on death? (should people die at home? hospital?)
8. What does it mean to say that somebody is "crazy"? (or **loco**?) Do you think it is an illness?
9. Have you ever known anyone who was **loco** or mentally ill?
10. What do you think are some of the causes of mental illness? (can it be cured? do you think such people should be hospitalized?)

PROBES: Enquire about: the eight folk illnesses described by Saunders; herbal cures and home remedies; hot/cold qualities underlying illness and cure; religious beliefs and practices related to health, illness and healing; attitudes about other "alternative" medical systems in Taos: naturopathy, homeopathy; lay midwives.

Figure 1.—Taos County Health Ethnography Interview Guide.

a therapeutic strategy in this otherwise strongly Catholic community.

Traditional Beliefs

Without probing during the initial interviews, only four of the 25 respondents mentioned any of the traditional Spanish-American folk ailments or beliefs. Interestingly, these were volunteered to one of the anthropologists and not to our Spanish-American assistant, who was perhaps the most curious about the extent of traditional beliefs and practices. This is not altogether surprising because ethnomedical beliefs constitute, especially among the Pueblos and Spanish-Americans of Taos, a sensitive area of investigation.* These beliefs and practices were often in the past ridiculed and suppressed by medical professionals and social workers who (regardless of their own ethnicity) were socialized into the professional orientations of Anglo culture.† Hence, without probing and demonstrating a knowledge of traditional beliefs, it is highly unlikely that much detailed information would be volunteered. At the end of the standardized list of questions, however, each of us *did* probe for traditional beliefs and practices, and this elicited a somewhat different picture.

Religious Influences on Health and Illness

When asked directly whether they thought that God or the saints had any influence over a person's health and well-being, 60% of the sample expressed the belief that God might *cause* illness for a variety of reasons, among them to punish sinners, to remind indifferent Catholics of His power and His existence, to bring lukewarm persons closer to Him, because "some people have to be sick to teach others a lesson" and because it is part of God's inscrutable plan. Three respondents (two of them Protestants) rejected God's role in sickness, two of them saying that illness was the work of the devil and the other saying that neither God nor the devil had anything to do with sickness. The remaining respondents subscribed to a more passive role of God in human affairs, saying that while He would not be the immediate cause of sickness, He certainly allowed it to happen.

Both observations (in churches, chapel and at religious processions and festivals in Taos) and open-ended discussions revealed that dedication to the Catholic saints is very strong, and both private and public devotions in honor of particular patron saints are often linked to petitions or thanksgiving for the healing of physical and emotional illness. The fulfillment of vows *(promesas)* for "special intentions," often concerning miraculous cures, brought many Taoseños to pilgrimage sites in various parts of the state. Each year, for example, hundreds of Pueblo Indians and Spanish-Americans of Taos County visit the famous *Santuario de Chimayo,* a healing shrine some 30 mountainous miles from Taos, to pray to *El Santo Niño* (the Holy Child of Atocha), Señor Santiago (the patron saint of Spain) or to Our Lord of Esquipulas (a miraculous image of the crucified "Black Christ"). The pilgrims partake of *tierra bendita* ("blessed earth"), a pit of healing mud found in a chamber to the left of the main altar. This mud is believed to possess many therapeutic qualities. It is said to cure (among other things) pains, rheumatism, sadness, anxiety, sore throat, paralysis and difficult childbirth. The pilgrims carry home small samples of the mud in bottles or handkerchiefs to give to friends and relatives at home. The blessed earth is dissolved in water and drunk or is smeared over the afflicted part of the body. In return the pilgrims and visitors leave small offerings and remembrances at the foot of the crucifix, statues and paintings of their patron saints: money, candles, pieces of handiwork, flowers, miniature hats, shoes and boots and even personal photos and identification papers.

Likewise, within the home and the community at large, devotion to Christ, the Virgin and the saints is expressed through lay membership in religious fraternities *(cofradias)* and in penitential brotherhoods *(penitentes),* which concern themselves with physical as well as spiritual discipline, healing and wholeness. Virtually every Spanish-American home has a small altar with an image or images of the Sacred Heart, the Infant of Prague and other, more local, saints. Traditionally, the *santos* (wooden statues) offered protection against witchcraft. "A medal of San Ignacio," offered one informant, "is a good protection against harm from others through the evil eye, bad thoughts or bad wishes and harm through [poisoned] food." Another woman said that "in the old days" there were many "superstitions" about the household *santos.* Among these were the beliefs that if a statue fell it was a sure sign that someone in the household was going to die, and that if one wanted to prevent a bad neighbor from slandering or telling lies, one could simply cover the mouth of a statue of San Ramon. Today, these beliefs are viewed as quaint superstitions, but faith in the healing power of the *santos* remains intact.

The Folk Illnesses

In probing for knowledge of specific ethnomedical beliefs, two thirds of the sample could adequately describe most of the eight folk illnesses reported by Saunders, whereas the remaining respondents could identify (with assistance) only the most commonly cited "naturalistic" ailments: *empacho, mollera caida* and *susto* (sometimes referred to, in this area, as *suspendido*). The respondents in this sample, however, added four folk illnesses not recorded by Saunders: *latido, insolacion* (or *asoleo*), *chincual* and *ajito.* Each will be briefly described in turn.

Mal de latido was described as severe and frighten-

*So sensitive an area is healing among the Pueblo Indians, for example, that an Anglo who married into and lived in one of the pueblos of northern New Mexico was not told by his own children (reared as Pueblos) the contents of their personal medicine bags that were always kept with them.

†The practice of *curanderismo* is outlawed in some states. The complete lack of cultural sensitivity of some clinicians toward ethnomedical practices was brought home to one of the authors who attended a pediatric conference in Texas where a paper was read on the traditional treatment of *mollera caida* (the infant held upside down and its head dipped into a dish of heated oil) as an illustration of what might be considered "potential" child abuse.

ing "palpitations" in the stomach. Left untreated, *latido* can be fatal. Because physicians do not recognize this illness, cure is traditionally effected by a *sobadora* (masseuse and manipulator of broken bones or displaced organs) who would massage a person's joints. An alternative treatment was for an herbalist or a *curandera* to soak bread in alcohol and herbs and tie it down firmly on the pit of the stomach while reciting prayers. No one reported a case of *latido,* however, in any of the interviews.

Insolacion (asoleo) was described as a kind of sunstroke causing the blood to "boil over" and "pound" in the head. The cure was to place a glass of water on a patient's head. When the water boiled (thus extracting the excess heat out of the body) the victim would recover. It was self-treated.

Chincual is a serious, blistering diaper rash covering the genitals, buttocks and thighs of an afflicted infant. It is attributed to deficiencies or excesses in the mother's diet or to envious and malevolent feelings on the part of another adult. Three cases of *chincual* were reported in this sample and were treated by a *médica* and an *albolaria.*

Finally, *ajito* was described as a cough or a cold in young children caused by allowing a child to run barefooted on a cold floor, which draws away natural body heat.

Whereas there was no evidence of an overarching philosophy of health perceived as a balance of "hot" and "cold"[12,18] natural elements, nor any vestige of cures based on restoring equilibrium through a judicious balancing of "hot" and "cold" foods, herbs or other *remedios,* as described by Saunders,[11,26] the logic underlying the folk illnesses *insolacion* and *ajito* is certainly that of temperature imbalance. In addition to these, it was believed to be foolhardy and tempting fate to gulp down large quantities of iced drinks when overheated, to iron clothes while barefooted or to go into the cold night air without a scarf or a wrap after working over a hot stove. In this last instance, a draft or gust of cold air can shock the body, resulting in temporary paralysis *(aigre),* freezing the mouth or the eye into a hideous position.

Although 17 of the 25 respondents could identify most of the traditional maladies of *curanderismo,* only 12 indicated (on direct questioning) a belief in one or more of them. Whereas virtually all the respondents could recall over their lifetime people (often their own parents and grandparents) who were said to have been cured of one or more of the folk illnesses, only a third of the sample (nine persons) had either themselves or an immediate family member (excluding parents and grandparents) been afflicted by or treated for a traditional illness in recent years (see discussion under Treatment of Illness).

The folk ailments that were most readily accepted by respondents as having some validity were those of "naturalistic" or "psychologic" origin, such as *aigre, melarchico* and *mollera caida,* or those that could be easily reinterpreted into biomedical or presumed scientific terminology. Hence, *aigre* was sometimes referred to as "just a cold" or an earache caused by drafts; *encono* could be described as a "bad infection," and *empacho* and *latido* as constipation and indigestion, respectively. *Melarchico* and *susto* were often translated as depression or "nervousness." The traditional diseases of magical or supernatural origin—*mal ojo* and *maleficio* were the most likely candidates for a flat rejection and denial by our informants or were interpreted as mental derangement. As one informant phrased it, "You'd have to be *loco* to believe in any of that stuff."

Nonetheless, *mal ojo* showed up about as frequently as other folk ailments in respondents' recollections of household illness episodes, and even those who flatly denied a belief in *ojo* or *maleficio* frequently qualified their statement with words to the effect that bad thoughts and feelings can adversely affect a person. As one young mother, a licensed practical nurse at the local hospital, put it:

> Of course, you don't want to really believe it, any of this nonsense. But *inside* you it just *feels bad* when you know that somebody wishes you ill. Just worrying about the jealousy or *maldiciones* [bad words, bad thoughts] of a friend or a neighbor is enough to make you sick.

Another 50-year-old grandmother said:

> Some of the old people here still believe, like the Indians, in witches. I don't believe in that but I do know that some people have a power that is unavailable to others. Some will use this power for evil. I don't believe in the evil eye, myself, but there *are* people that have 'strong eyes' and can influence others with their looks. One is a young 'playboy' type who looks at innocent young girls in a way that they lose all will power against him. Another is an old man from Mexico. And right here in Rios there is a young woman who was beaten terribly by her mother all her life. I guess it was what they would call 'child abuse' today. Everyone knew about it, but no one interfered. It was a prominent family. Now the girl is grown up and is a mother herself. She is an evil-tempered person, and neighbors are afraid of her and her 'strong' eyes.

The old woman paused in the telling, and added with contemporary psychologic insight, "Perhaps they just feel guilty, and don't want to look her in the eyes."

Overall, there was a tendency to view sickness and health in strongly personalistic and interpersonal terms. Human encounters can sicken a person, even unto death. Qualities of personal magnetism evidenced in the attraction between a stranger and a vulnerable infant *(mal ojo),* in sexual charisma and charm (that "bewitches" a lover) and in the extreme attachment of a child for its absent mother *(melarchico)* are strong pathogens within this system. Likewise, qualities of personal antagonism, hostility or simple physical incompatibility can result in illness. A shopkeeper from a small agricultural hamlet outside of Taos explained this quite succinctly:

> It's like this: when people meet sometimes they attract and sometimes they clash. One person can be like poison ivy to another one. There is a repulsion, something like an allergy, of one to the other. When they meet the blood of the weaker one overreacts and the person can break out in a rash, or hives, in an itch, or even worse, he can become badly infected. We say he has become *enconado.* I knew of a case where a selfish child was enjoying an ice cream cone in front of two of his

friends without even offering them so much as a lick. Well, the next day his mouth was covered with blisters. They fixed him! Sometimes you don't *mean* to do it; it just happens. That's why we take special precautions not to visit someone at home who has just recently returned from an operation. Even when we are invited we say, 'No, no it is still too soon for a visit. The wound has not yet healed.' We are afraid of starting an infection.

Of all the folk ailments discussed by our informants, only *mollera caida* ("fallen fontanelle") was accepted as a valid illness in its own traditional terms by most of those interviewed, with no attempt made to reinterpret the syndrome in medical or psychologic terms. As the young nurse cited above said: "I didn't believe in *mollera caida* until I saw so many cases in the hospital *with my own eyes.*" This pediatric ailment continues to be a source of worry for the poorer young mothers of Taos County.

Treatment of Illness

In the course of respondents' answers to specific questions and in their more open-ended discussions of illness beliefs and practices, the 25 respondents discussed a total of 147 illness episodes experienced by themselves or a family member in recent years (excluding pregnancies and uncomplicated deliveries, despite the fact that many respondents viewed normal pregnancy as a kind of illness). It should be noted at the outset that the reporting of many of the illnesses occurred in the context of an interviewer probing for vestiges of folk illness beliefs and the practice of *curanderismo.* Hence, there was a decided bias toward informants' recalling the more deviant and dramatic incidents of folk illness. The respondents themselves roughly categorized the illnesses into *mild* or *minor* (those that were treated within the family and with over-the-counter drugs or home remedies) and *severe* or *serious* illnesses (conditions warranting a consultation with a medical specialist, either professional or "folk").

In all, 64 illnesses were judged to be mild, 42 of which were described in standard lay terms and 22 using Spanish-American folk terms. Whereas each of the 25 respondents indicated at least one episode of a common "biomedical" ailment, only nine informants accounted for the 22 folk diagnoses (see Table 2).

The most common *remedios* for these mild illnesses (whether standard or folk) were prepackaged over-the-counter drugs: aspirin, antacids, tonics, laxatives and vitamins. Only 11 of the respondents indicated that they occasionally used a home or herbal remedy. When they did, they were equally likely to use an herbal tea for a common cold as for *aigre,* and a poultice for a migraine headache as for *encono.* The most frequently mentioned herbal medicines in our sample were: *altamisa* (mountain mugwort) for colds and flu; *cota* (Navajo tea) as a diuretic and also to settle the stomach and purify the blood; *alegria* (amaranth) for mild heart disorders in old age; *osha* (porter's lovage) for bronchitis, colds, *aigre* or fever; *chamiso* (sagebrush) for flu, breaking a fever, stomach pain or *empacho; poleo* (brook mint) for feverish headaches,

TABLE 2.—*Mild, Self-Treated Illnesses*

Standard Terms (N = 42 illnesses in 25 households)		*Folk Illnesses (N = 22 illnesses in 9 households)*	
Upper respiratory tract disorders (colds, coughs, flus, etc)	17	*Aigre*	6
Sores, infections	6	*Encono*	4
Gastrointestinal (diarrhea, stomach trouble, gas, etc)	6	*Mal ojo*	3
Bleeding	6	*Susto*	3
Fever	4	*Melarchico*	2
Heart trouble	1	*Empacho*	2
Arthritis	1	*Chincual*	1
Insomnia	1	*Insolacion*	1

dizziness, colic and *mal ojo* in infants; *malva* (cheeseplant) for sore throat, skin rash and *chincual,* also as a douche and to help expel the afterbirth; *peyote* for anxiety; *ruda* (rue) to stimulate menstruation when delayed and as an abortifacient, and the Spanish-American herbal aspirin, *manzanilla* (chamomile) for colds, fever, stomach problems, menstrual cramps and earache. With the exception of peyote, these most common herbs and dozens more are available in the back of a pharmacy in the Taos town plaza. Many were sold out at the time one of us (N.S.H.) purchased samples in the summer of 1983 and the pharmacist volunteered that business in prepackaged and dried herbs was brisk. Also available at the pharmacy was a helpful booklet on the use of traditional herbs, flowers, roots, barks and gum.[27]

In all, 83 conditions or illnesses were described by the respondents as serious, resulting in a consultation with a physician, dentist, nurse-practitioner or traditional healer. In all cases our respondents, at least initially, took their serious nonfolk illnesses to a physician or medical clinic. All but three of the 25 respondents had a regular family physician whom they consulted when they were feeling more than mildly ill. By contrast, none of the respondents considered themselves the "regular patient" of a specific traditional curer. Physicians, clinics and hospitals constituted the respondents' primary sources of medical care. In evaluating local medical services, respondents were, with two exceptions, enthusiastically favorable about the quality of care received. In discussing recent episodes of serious illnesses in 52 of the 83 episodes reported, treatment began and ended at a medical clinic, physician's office or hospital under the care of a standard medical practitioner (Table 3).

The general impression received by the field-workers was of a relatively self-sufficient rural population, most of whom respected physicians and standard medical care, but who tended to reserve medical consultations for relatively serious or chronically bothersome disorders.

While each of the 25 respondents volunteered at least one recent household illness serious enough to warrant a medical consultation, nine of the 25 had also, in recent years, consulted a traditional healer for a member of the household. Of the 31 consultations

reported (Table 4), 21 were for serious or persistent cases of a folk illness and 10 were for nervousness, aches and pains and bronchitis. More than a third of the visits to a folk practitioner concerned childhood illnesses.

The practice of *curanderismo* in this region is of a pragmatic and naturalistic bent in which the use of herbs, the regulation of diet, massage and the manipulation of bones and joints predominate over the use of charms, incantations and magical cures. Rather than folk psychiatrists who treat only psychogenic disorders (and folk illnesses), as has been previously suggested,[5,7,17] the *médicas* and *curanderas* of Taos can be more accurately described as general folk practitioners or possibly as folk pediatricians who treat a broad spectrum of acute and chronic ills.

TABLE 3.—*Conditions Treated by a Physician or Health Professional* (N=52 Illnesses in 25 Households)*

Operations	8
Pain/headaches	6
Accident related	5
Upper respiratory tract disorders	5
Gastrointestinal problems	4
Dental work	4
Cardiovascular problems	3
Diabetes mellitus	3
Tension, "nerves"	3
"Real sick"	2
"Fevers"	2
Mollera caida	2
Susto	2
Aigre	1
Allergy	1
Sore eyes	1

*Excluding obstetric visits, diagnostic examinations and checkups.

TABLE 4.—*Consultations With Folk Practitioners in Taos County* (N=31 Illnesses in 9 Households)*

	Practitioner Consulted		
Illness	*Médica/ Curandera† (Folk Healer)*	*Sobadora (Traditional Masseuse and Bone-setter)*	*Albolaria (Herbalist)*
Mollera caida	5	..	..
Empacho	3	1	..
Muscle aches and pains	..	4	..
Witchcraft cure	..	..	2
Susto	3	..	..
Mal ojo	2	..	1
Chincual	2	..	..
Nervousness	..	2	..
Encono	1	..	..
Aigre	1	..	..
Bronchitis	1	..	..
Abdominal pain	1	..	..
Migraine headaches	1	..	..
Earache	1	..	..
TOTALS	21	7	3

*Excluding *parteras* (midwives).
†The feminine form of the names is used because at the time of the study all of the Spanish-American folk healers in Taos County were women.

The pragmatic approach is reflected in one woman's account of the successful treatment of her infant son's serious bout of colic by a *médica* who diagnosed the problem as *aigre,* too much air entering through the baby's navel. The *médica* suggested frequent abdominal massage with warm olive oil and she put a paste of raisins and cinnamon in the navel to prevent further "drafts." The baby's condition improved in a few days.

Somewhat surprisingly, there was no correlation between age, education, social status or occupation and use or nonuse of a folk practitioner. The nine respondents who had, or whose family member had, made some use of a traditional healer averaged 44 years of age (range, 16 to 79), slightly younger than the sample at large, included one man, and represented a variety of occupations that included full-time student, social worker, housewife and mother, religion teacher, typist, day-care teacher and maid. One factor, however, was significantly correlated with the use of a folk practitioner. In all the cases reported here the client knew the healer in other nonmedical social contexts. Often the *médica* was a relative, neighbor or fellow parishioner. Relations through godparenthood linked some persons to *curanderas* and in at least one case coparent ties brought a Spanish-American client to treatment by a Pueblo Indian medicine man living at the Taos pueblo.

The degree of medical pluralism within this culturally heterogeneous region is reflected in the five respondents who preferred the care of a physician to a traditional curer for isolated cases of *susto, mollera caida* and *aigre.* One middle-aged woman, for example, praised the weekly injections given her by an Anglo physician in Santa Fe for her chronic case of *susto.* Another, a young mother, explained that it was not necessary to take an infant suffering from *mollera caida* to an "old-fashioned" *médica* when there was nearby a Spanish-American physician who knew exactly how to push up on the soft palate to bring it back into place, while also prescribing necessary medicine for the child. Similarly, not all the *curanderas* and *médicas* mentioned by respondents were Spanish-American. One young *curandera* judged by some respondents to have an exceptionally broad knowledge of local healing herbs is an Anglo lay midwife, while another *médico* was a local Pueblo Indian medicine man. Finally, a black woman healer from Albuquerque had been visited on several occasions by one respondent.

The climate of cultural tolerance appears to have affected the self-selection of the 22 physicians practicing then (1979) in Taos County, most of whom were, like the *curanderas,* general practitioners rather than specialists. A few of these worked rather closely with members of the Taos County Midwives Association, a group of largely self-trained and countercultural lay midwives. Other physicians have integrated aspects of homeopathy, naturopathy, Native American spiritualism and Eastern mysticism into their practice of biomedicine. These are a small but very visible minority of the physicians. Possibly because the traditional Spanish-

American practitioners are elderly and do not actively seek it, there was no ongoing referral system between physicians and *médicas,* though *médicas* in Taos (as recorded elsewhere in the West and Southwest) frequently refuse cases that they believe should be handled by a physician.

With the help of key informants we were able to identify six Spanish-American traditional practitioners: two *médicas,* one *sobadora,* one *albolaria* and two *parteras.* However, with the exception of the nine persons whose families had occasionally used them in the past, most of our sample could not identify more than one or two of them by name. And, while home birth with a midwife is becoming increasingly popular among Anglo residents of the Taos area, Spanish-American mothers prefer the privacy and accommodations of Holy Cross Hospital in Taos. Only four women of the 20 in our sample had consulted a traditional *partera* for the birth of any of their children, and these women were all middle-aged or older, representatives of the prehospital era of rural Taos County.[28] The home birth ethos of the young Anglos who have recently migrated to Taos[29] was uniformly rejected as backward and primitive by the several young Spanish-American mothers in our sample.

Conclusions

. . . . All the poor sick people waitin'.
So many ways of being sick.

TILLIE OLSEN, 1974[30]

The findings of this exploratory study are compatible with those of other recent studies of the state of Spanish-American folk medicine in the West and Southwest today.[8,18,31] Time and acculturation seem to have greatly eroded the belief in and practice of *curanderismo* that was posited as the predominant medical system of Spanish-Americans in New Mexico, California and Texas just two or three decades ago.[6,11,12] Nonetheless, the recent criticism of the romantic "primitivism" of anthropologic studies of Spanish and Mexican-American culture and social institutions is perhaps overstated. While we could infer from our findings that *most* Spanish-Americans of Taos County rely primarily on the same explanatory model as Anglos with regard to the definition of health and illness, the perception and meaning of symptoms and lay theories of disease causation, at least some elements of *curanderismo* are supported by the population. Among these we would list a strong religious interpretation of the meaning of sickness, a belief in the pathogenic nature of strong emotion, a tendency to attribute unexplained physical or emotional malaise to troublesome or malevolent interpersonal relations and a belief in the salutary effects of balance and moderation in behavior, feelings and human relations.

In contrast, however, to Saunders's generalizations about the strength and pervasiveness of Spanish-American folk medicine in Taos County, we would have to conclude that *curanderismo* in northern New Mexico today has moved from being a primary and important source of medical care to an alternative and very occasional source in cases of chronic pain and illness or for those puzzling psychosomatic and stress-related afflictions for which biomedicine has little respect and virtually no cure and therefore for which it has none of the creative names and faces that the folk medical system readily supplies. As long as this medical vacuum exists, we predict it will be filled by alternative systems such as *curanderismo.* In addition, the cultural heterogeneity of Taos County, the characteristic blending of old and new traditions and the enormous pride of its residents—Spanish-American, Native American and Anglo—in the distinctiveness of Taos from the rest of America, virtually assure that *curanderismo* will survive the 20th century.

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Ethnic Elders and American Health Care—A Physician's Perspective

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The aging process is a fugue composed of innumerable themes; the theme of "ethnicity" is by far one of its more dominant. Due to the increasing incidence of chronic, progressive infirmity and acute, catastrophic illness, the elderly are thrust into direct contact with the health care systems of their society. The experiences of ethnic elders in American health care situations are fraught with conflict and mutual dissatisfaction with the physician-patient relationship. Both providers and consumers of health care services harbor differing culture-bound perceptions of health, illness and the healing process; these cultural beliefs define personal and professional needs and expectations and notions of how those needs are to be met by others. Both physicians and patients can enhance their communication and their compassion for one another by acknowledgment of cultural differences and by increased willingness to interpret motives and behavior within native context.

It behooves us in medicine to examine the cultural traditions underlying our own attitudes, beliefs and values about the aged in a universal sense, as well as in a culturally specific sense, that we may gain insight that will be helpful in serving elderly persons more effectively, and in solving some of the problems inherent in the aging process.

Most physicians will remember with great emotion, as I do, the day of graduation from medical training; amidst the hooding, handshaking and celebration, a solemn oath was taken,

> [to] maintain by all the means in my power, the [integrity] and the [worthy] traditions of the medical profession . . .
>
> not [to] permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient . . .
>
> [to] maintain the utmost respect for human life . . . even under threat, I will not use medical knowledge contrary to the laws of humanity . . .[1(p373)]

My graduation was a time of believing that modern medicine as taught and practiced in Western civilization transcended all other forms of healing in technical skills and scientific understanding; that physicians as guardians of this realm would bestow health upon the masses in such a way that any rejection of care by a patient could only be interpreted as ignorant or ungrateful.

A disturbing revelation occurs to neophytes soon after being on the frontlines of medical practice: considerations of religion, nationality, race, party politics, social standing, gender and age—not only of one's own but also that of patients—primarily affect the physician-patient relationship within which the processes of therapy intending to restore health may take place. At best, there is a coming to grips with the fact that both provider and consumer of health care services harbor differing culture-bound perceptions of health and illness, and of how respective needs and expectations are to be met.

Professions within a society contain not only a set of techniques for doing useful work (skills), but also a set of beliefs, values and traditions (knowledge), and so may function as cultures in their own right. Medicine is undisputably a prototype of the professions in this regard, one that is also able to perpetuate itself via an educational system designed to ensure the enculturation of successive generations. This concept has

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ABBREVIATIONS USED IN TEXT

CCU = coronary care unit
CT = computed tomography

been discussed thoroughly elsewhere and will not be pursued here, other than to lay the premise.[2-4]

The focus of this article is the experiences of ethnic elders in American health care settings, with my purpose being to examine the differing culture-bound perceptions of both providers and patients in operation; to witness the manner in which beliefs and traditions in conflict are resolved, and to infer significant impact on the quality of the therapeutic encounter.

Reports of the medical cases of four older persons from major US ethnic backgrounds will be given, each case chosen for its rich illustration of the respective cultural values in conflict with the values of modern medical culture. Name initials of these patients have been used to preserve anonymity. My perceptions derive from these relationships and many others during my medical training as an internist and as a geriatrician and from exposure to the clinical and theoretical work of gerontologic researchers. I must state from the outset my awareness of the prevailing sensitive viewpoint in the gerontologic literature that it is difficult to assess the singular force of cultural factors within the process of aging.[5-11] I concur that the factors of "ethnicity," "minority status," "gender roles" and "socioeconomic class" are separate but additive dimensions of the aging process. To the extent that it is possible to identify cultural factors per se, I have approached each case presentation with the hindsight of a quarterback determined to learn new strategies.

Reports of Cases

Case 1. FC, a 70-year-old Mexican-American, Spanish-speaking woman, was admitted to an acute care hospital due to coma of unknown cause. She had been found unresponsive in the vineyards, in 40°C (104°F) midday heat, where she had been picking grapes alongside family members earlier that day. The patient was reportedly in good health before this event, though there had been complaints of dizziness and "passing out" during the previous week, unwitnessed by the family. It was thought that she might have had diagnoses of "high blood pressure" and "diabetes" in the past; however, the patient was not known to be under the care of a regular physician, and it was certain that no medications had been taken for at least a year before admission. There was no history of cardiac, pulmonary, thyroid or renal disease. FC was a nonsmoker and drank nonalcoholic beverages only. She had immigrated to the United States from Mexico as a farm laborer some 30 years earlier, and had recently come to live with her eldest daughter in a rural farming community in California. The family requested that everything possible be done to restore her health.

On admission physical examination she was deeply comatose but breathing spontaneously at a rate of 28 per minute. Blood pressure was 190/100 mm of mercury, pulse 120, rectal temperature 38.3°C (100.9°F). Pertinent findings included the following: pupils were pinpoint, unreactive to light and tonically deviating to the left on cold calorics. The neck was rigid. Cardiac rhythm was regular with a systolic murmur grade 2/6, loudest along the aortic axis, radiating to the base of her neck; carotid upstrokes were full, with normal contour. Bilateral carotid bruits were present. Neurologically, she presented with a Glascow coma score of 7—unresponsive to deep pain, with absent reflexes. A left-sided Babinski's reflex was present. Laboratory studies showed an elevated leukocyte count with left shift and an elevated glucose level without ketosis. A computed tomographic (CT) scan of the head showed mild frontal atrophy; there was no space-occupying lesion. Chest x-ray film showed a prominent left lower lobe infiltrate. Other conditions ruled out were acute myocardial infarction, myxedema coma, nonketotic hyperosmolar coma, meningitis, adrenal crisis and status epilepticus. The initial working diagnoses on admission were massive left hemispheric stroke and aspiration pneumonitis.

On the second day after admission, an endotracheal tube was inserted and the patient was placed on mechanical ventilation after sudden respiratory arrest. Because blood pressure was not adequate, central lines (venous and arterial) were placed and a dopamine hydrochloride drip was begun. Full supportive measures were given, including fluid and electrolyte replacement, antibiotics and insulin. On physical examination on day 6 she had fixed, midpositioned pupils, absent doll's eyes, complete areflexia and no spontaneous respiratory effort for 120 seconds supported by mechanical ventilation. Two electroencephalograms taken on consecutive days recorded the absence of brain wave function.

The criteria for brain death established by Harvard, the University of Minnesota and the National Institute of Neurological and Communicative Disorders and Stroke Collaborative Study were satisfied no later than day 8.[12-14] According to the California Brain Death Statute, "the patient shall be pronounced dead if it is determined by a physician that the person has suffered a total and irreversible cessation of brain function."[15] The medical team therefore announced to the family that the patient was to be pronounced dead and that all supportive measures were to be stopped.

The family, weary from an eight-day vigil at the hospital, was unprepared to receive this declaration. Chaos ensued—20 men, women and children, weeping and shouting angrily in Spanish and nonfluent English, but their message was unequivocally "Do not stop resuscitative measures." Initially, the medical house-staff team interpreted this response as "appropriate hysteria, expressing grief and denial of death." Several hours later, the family's disbelief was voiced more clearly at the bedside: "What is the meaning of 'brain death'?"

To them, the patient appeared to be asleep, her body still warm, heart still beating, lungs still breathing and a leg or arm twitching every so often; how could she possibly be dead?

The medical house staff was annoyed by the delay caused by these simplistic questions, especially because full explanations had repeatedly been given to them: (1) the patient was still warm because the blood pressure was being maintained pharmacologically with pressor agents so that perfusion of her tissues was adequate; (2) spontaneous cessation of heartbeat within a few hours or days usually occurs in patients with brain death who are receiving respiratory ventilation and supportive care of vital functions[16,17]; (3) the machine was forcibly exchanging air in the patient's lungs and was "breathing for her," and (4) her limbs still moved due to random "peripheral reflex spinal arcs" severed from upper motor neurons. So why could not these people understand that "she will never wake up"? The house staff was further outraged that here was a patient certainly not benefiting from continued care, yet allowed to divert precious medical resources by the "selfishness" and "ignorance" of the family members. Eventually, the medical house staff could not justify to the Hospital Review Committee the prolonged occupation of a bed by a dead patient. Thus on day 10, the patient was pronounced dead and the equipment was removed. The only further discourse between house staff and family was the information that the body had been transferred to the morgue where they would later be able to claim it.

Discussion. This woeful breakdown in communication might possibly have been averted had someone perceived the dynamics of several major cultural issues in this situation. The Mexican-American culture has different expectations of the therapeutic relationship, based on the *curandero* model. These folk curers are expected to be warm, friendly and interested in all aspects of a patient's life. Western medical practitioners have been taught that impersonal objectivity is a vital part of a physician's role as an applied scientist. In addition, physicians tend to value efficiency of time and of energy, a survival trait reinforced by years of heavy clinical duty in postgraduate medical training programs. Thus, dispensing with social congenialities and "getting down to business" may be examples of emotional economy and time efficiency, whereas in the Mexican-American culture, efficiency of any kind is not a particularly admirable trait.[18] Rather, the impersonal objectivity and efficiency that typify the clinical manner of a Western physician can seem imperious and even rude to people who are familiar with different norms of behavior for their therapists.

Mexican-American families take a much more active role in the medical care of family members. Patients usually do not make their own medical choices without their relatives assisting in the decision-making process, whereas physicians assume that the special training they have received qualifies them to take authority and to render decisions alone; they do not expect to be challenged by patients or other health care professionals.[19]

The language barrier was definitely a factor contributing to poor communication, as was the use of technical terminology laden with medical jargon.[20] Pride and shyness may prevent Spanish-speaking patients from reiterating pertinent questions until meaningful answers are obtained.

Beyond these discussed cultural barriers to effective relating, this case highlights yet a more subtle issue of cultural content, that of defining "the seat of self." Modern medical professionals believe that the brain contains the essence of who we are—our personality, drives and consciousness itself. The brain innervates and ultimately controls all thoughts, muscles and organ function. Loss of brain function is equated with loss of purposeful life. Contrarily, the Mexican-American culture holds to a more holistic view of being and personhood in its belief that mind and body are inseparable.[21] The soul of a person dwells nevertheless in one who sleeps, or appears to be asleep.

Looking again at this case, one can see that this family carried an enormous burden to act on behalf of their elder in her comatose state. Had the family been approached by a more courteous, empathic medical team, seeking the family's counsel and cooperation during the ten-day hospital course and using bilingual interpreters to insure optimal communication, a relationship of mutual trust and goodwill might very well have been established. In the safety and strength of such a bond having been developed between care providers and family participants, the sensitive exploration of the idea that the patient would never regain former health and consciousness might have resulted in a joint decision to terminate supportive care.

Case 2. JR, a 75-year-old Mexican-American, Spanish-speaking woman, was admitted to a coronary care unit (CCU) to rule out an acute myocardial infarction. She had had symptoms of muscle aching of the entire body, especially the chest, head, neck, back and right knee, persistent for the past three days. She noted the onset of increasing exertional dyspnea and fatigue about a year before. She specified that she had not had antecedent hemoptysis, sore throat or skin infection. Coronary risk factors included hypertension "for many years," though she had not seen a physician in the past ten years and was currently taking no medicine. She had no medical history of diabetes mellitus, cigarette smoking, family history of early cardiac events or lipidemia. In the past she had had similar bouts of total body aching, chest tightness and fever, beginning in her childhood in Mexico, at which time she had been told by the village *curandero* that she had been "bewitched."

At the time of admission, the elderly patient was obese and appeared anxious. Blood pressure was 180/90 mm of mercury, her pulse was 92 beats per minute, respirations 22 and she was afebrile. Abnormal findings were mild congestive heart failure with scant bibasilar lung rales. Cardiac rhythm and rate were regu-

lar with a prominent diastolic murmur, the typical rumbling and opening snap of mitral stenosis. Serial electrocardiograms showed nonprogressive anterior ST elevation and T-wave inversion, and serum creatine phosphokinase isoenzyme studies were negative, ruling out an acute myocardial infarction. Antistreptolysin-O titer was pending. As the patient improved clinically with diuresis, pulmonary arteriogram or lung scan to rule out acute pulmonary embolism was not done.

JR had recently moved to California from Texas to live with a daughter and her family. The present family situation was described as "stressful" and the patient's illness was causing more disruption. She interpreted her own symptoms to mean that she was "being warned" that she was in danger while living with her daughter. While the patient was in the CCU, the family visited daily; however, they were not allowed to stay at the bedside for more than five minutes per person, once in the afternoon and once in the evening. The family brought field flowers to place on her bedstand, and these were immediately removed by the nursing staff after their departure, as flowers carrying insects and dander were not permitted. The family brought home-cooked food for her, but the medical staff would literally take it out of her mouth, as she was on a strict CCU protocol that did not allow eating in the first few days of an acute coronary event. No singing or praying aloud was permitted in this unit. Physical contact with the patient was nearly impossible as she was entangled in electrocardiographic leads, oxygen cannulas and intravenous tubing, disruption of which triggered the ascent of alarmed nurses to the bedside, blaming the bystanders for disturbing the patient's healing process. By the end of the hospital stay, JR was convinced that her family did not care about her welfare or her recovery. There also was an element of magical ideation in her perceptions that the flowers and foods had "vanished" from the bedside; though the family had made attempts to support her, their efforts were thwarted by "evil" spirits.

The house staff approached the patient with a full explanation of her probable history of rheumatic fever and the sequela of valvular heart disease—mitral stenosis—and offered her the option of mitral valve replacement. She sharply dismissed them, saying that she was returning to Texas, which would put an end to her symptoms. The medical house staff was on the verge of calling for psychiatric consultation for this elderly woman who appeared to be expressing bizarre thoughts and refusing irrationally a lifesaving procedure—to evaluate whether she was displaying a variant of "intensive care unit psychosis" and stimuli deprivation.

Discussion. In discussing the cultural issues inherent in this situation, I will describe further the folk beliefs of the Mexican-American culture mentioned in the previous case. A patient is seen as the passive recipient of disease; patients themselves are blameless, as disharmony is the work of witches or evil spirits. The power wielded by *curanderos* is not so much that of cursing or appeasing these spirits, as it is that of emphasizing the *curanderos'* connections with the sacred and using skills to interpret the significance of the imbalance between a patient and these external forces. Perhaps JR had earlier in her youth received from a *curandero* a similar interpretation of the periodic relapses of her illness: sickness was a warning of immediate danger in her environment.

Our medical culture values sterility, meticulous order and quiet in the healing environment, and intensive care units are notorious for their enforcement of regulations to insure sterility, order and quiet—in some cases, much to the detriment of patients who believe the healing process to be a time of increased family attention, rather than abnegation. Had the house staff recognized the disparity between the outer appearance of this elderly woman, whose body submitted to "protocol" without complaint, and the inner reality of cultural beliefs processing the events of the natural and supernatural world, some effort would have been made to reconcile the family and their elder parent, and to facilitate what may have been primarily an adjustment reaction to residential relocation and reintegration into the family structure.

Case 3. HL, a 66-year-old Chinese-American man, was admitted to hospital with symptomatic hypocalcemia of undetermined cause. He had been in his usual state of good health until about 12 months before admission, when fatigue, abdominal cramps and muscle aching began. The patient treated these symptoms with acupuncture and a variety of Chinese herbal medications, and believed these to be efficacious. Two weeks before, he had a viral syndrome with loose, nonbloody stools, resolving after one week. On the morning of admission, HL awoke with frank carpopedal spasms, unrelieved by acupuncture or herbal teas. His admission serum calcium level was 6.4 mg per dl (normal, 8.5 to 10.5), with normal serum phosphorus, magnesium and albumin levels.

He had not had a neck operation, renal disease, alcohol abuse, chronic diarrhea or pancreatitis, nor had he ever taken medications associated with hypocalcemia, such as anticonvulsants. There was no family history of parathyroid, adrenal, thyroid or ovarian disease, or pernicious anemia. His diet contained a meager amount of milk or dairy products; the patient said that he had never liked these foods and so avoided them. HL had immigrated to America from Canton in his early 20s and had married a Chinese bride in this country. He had been employed as a restaurant cook for the past 25 years, supporting his wife and three sons.

On physical examination, he appeared to be younger than his stated age of 66 years, was well developed, slender and short statured, with no obvious skeletal abnormalities. There was a positive Chvostek's sign (tapping the facial nerve produced a contraction of the facial muscle) and a Trousseau's sign (tourniquet-induced spasm of the forearm). The initial tetany had been terminated in the emergency room by the intravenous administration of calcium gluconate. X-ray

films taken during the hospital course did not show osteoblastic disease or basal ganglia calcification. There was no clinical or laboratory evidence of rhabdomyolysis or renal failure. Determinations of serum vitamin D and parathyroid hormone levels and fecal fat values were pending. As HL did not progress to more serious complications such as convulsions, he was discharged with the recommendation to take calcium tablets, and encouraged to increase his dietary intake of milk products.

The patient returned to medical clinic in one week for follow-up examination. The serum calcium value was then 7.4 mg per dl with a normal phosphorus level. Latent carpopedal spasms were evident. He informed the clinic team that he did not take any of the calcium supplements, nor did he alter his diet to include more milk products. Several clinic visits later, the medical team members became more exasperated by the futility of their efforts to improve the patient's condition, and they began to describe this patient as "noncompliant" and "stubborn," and to hold him responsible for prolonging his illness. HL missed the next two consecutive clinic appointments. Subsequently, the results of the vitamin D and parathyroid hormone levels returned as high-borderline normal and low, respectively. The 24-hour fecal fat was quantified as greater than 5 grams, suggestive of a malabsorption syndrome.

A clinic physician called HL to ask him why he had not kept his clinic appointments and to discuss the necessity of obtaining more tests to rule out small bowel disease as the cause of intestinal malabsorption; fat malabsorption would cause a subsequent decrease in vitamin D (as well as other fat-soluble vitamins) stored in the body, thereby altering calcium balance. The patient was very reluctant to return to a health care setting to be chastised for noncompliance with a regimen that he could not accept. Furthermore, he was reluctant to undergo any invasive testing. He explained that milk and dairy products were not prominent foods in the Chinese cuisine and, to his knowledge, had never been. The patient had enjoyed relatively good health all his life, and he felt that it was "unnatural" to begin at the age of 66 to ingest each day 14 pills of assorted calcium carbonate, magnesium oxide and vitamin D_2.

Discussion. There are several cultural issues to be reckoned with in this case of seemingly polarized wills. Traditional Chinese medicine avoids intrusive techniques such as venipuncture, surgical procedures and contrast radiology; and diagnoses conditions relying exclusively on astute history taking and physical examination.[22] Western medicine attracts students who enter medical schools with the highest of social values, but who emerge into practice idealizing advanced technology. Our economic reimbursement system and the Western consumer's technophilic beliefs have certainly reinforced this shift in value system to one that deprecates interpersonal skills in favor of physical technologic skills, including greater reliance on acute and pharmacologic interventions rather than long-term, interpersonal interventions that are primarily needed to manage the chronic conditions of the aging process and population.[23] As HL was not bothered with severe symptoms of calcium deficiency, he was content "to leave well enough alone" and not to cooperate with unnecessary tests or technologic procedures. He reasoned that acupuncture was best in treating yang (intestinal) conditions, and so he would continue to apply this method of maintaining health.

Traditional Chinese medicine also views the body as a gift given by parents and forebears. Not being our personal property, the body must be cared for and well maintained. Confucian teaching states "only those shall be truly revered who at the end of their lives will return their physical bodies whole and sound."[21] Ethnographic research asserts that Chinese-American patients want very much to understand their illnesses, to know the cause of the illness and how that cause is linked to symptoms.[24] For a medical team of Western-trained nurses, physicians and dietitians to accuse this Chinese-American elder of noncompliance was more than mere insinuation that he was not taking care of himself or not interested in his health—it was a direct personal and ancestral insult. One wonders if wounded pride prevented him from trusting the physician enough to proceed with more invasive investigation in the pursuit of a definitive diagnosis.

Lactose intolerance due to lactase deficiency has an incidence in American blacks, Bantus and Asians as high as 80% to 90%.[25] This phenomenon of nature may in part be responsible for a culturally conditioned aversion to milk products in these racial groups.[26,27]

Successful resolution of this conflict pivoted on the acknowledgment to the patient that his condition was a momentary imbalance of the *yin* and *yang* forces* and that the taking of these nutrients could not only restore balance, but also prevent disease. It was suggested that he crush the calcium, magnesium and vitamin D tablets to a powder form (fortuitously it resembled ginseng powder) and drink it as a slurry. This method proved to be highly acceptable to him, possibly because other popular Chinese remedies include ingestion of pulverized sea horses for the treatment of gout and ground deer antlers for the treatment of impotence.[21]

HL was grateful to hear that it was not necessary to change his dietary habits so long as he maintained the preventive practice of drinking the calcium slurry that he prepared fresh daily. Both physician and patient were elated by the gradual rise of the serum calcium level into the low range of normal and the disappearance of fatigue and muscle aching. I suspect that spiritual well-being as well as physical (chemical) balance had been achieved, as the patient later consented to undergo a small bowel series.

CASE 4. NT, a 78-year-old Pilipino† man with

*In Chinese cosmology, *yin* is the passive principle exhibited in darkness, cold and wetness; *yang* is the active principle exhibited in light, heat or dryness; the two forces combined produce all that is.

†The spelling "Pilipino" to designate a person of Philippine ancestry corresponds to the usage adopted by the national language of the Philippines.

known prostate cancer, metastasis to the ureters and chronic renal failure due to obstructive uropathy, was admitted to hospital for the evaluation of abdominal pain for several weeks. This midepigastric pain was described as dull, unrelenting in every position, sometimes eased by milk. He had no history of peptic ulcer disease, alcohol abuse, chronic pancreatitis or gallbladder disease.

The patient had immigrated to the United States from the Philippine Islands in the 1930s, finding steady employment as an agricultural laborer in the fields and canneries of the Pacific West Coast. At the age of 50, he married a Pilipino woman 20 years his junior and fathered two daughters and one son. His wife had died swiftly of ovarian cancer within the past year, after heavy reliance on the home help of the daughters who were both married and had families of their own. The son, the youngest child, was in military service and was unable in recent years to participate in family dynamics.

On physical examination, NT was cachectic, frail and appeared to be quietly enduring severe pain. His abdomen showed a right lower quadrant pulsatile mass and a palpable mass in the epigastrium, also pulsatile with a bruit. Laboratory studies at the time of admission showed the following values: blood urea nitrogen 98 mg per dl, serum creatinine 5.3 mg per dl, potassium 5.1 mEq per liter, hemoglobin 12 grams per dl and hematocrit 37%. Results of an upper gastrointestinal series to rule out peptic ulcer disease were entirely within normal limits. Abdominal ultrasound studies ruled out abdominal aneurysms; the radiologist noted a tortuous distal aorta proximal to the bifurcation. A solid homogeneous mass 4 cm by 5 cm was located in the region of the pancreas. A CT scan of the abdomen showed a pancreatic tumor in the head and body of the pancreas. Surgeons felt that the patient was a poor operative risk for pancreatic biopsy under direct visualization. His prognosis was grim and his total care needs in his time remaining were immense. The daughters were well acquainted with the burden of total care-giving to a dying patient, having recently cared for their mother at home before her death. In fact, they were still utterly exhausted and their families that included small children were still recovering from the ordeal. The prospect of now having to bear full responsibility again, this time for their father's terminal care, was nearly unthinkable.

The ward social worker was adamant that the daughters "be honest" with their father and tell him that they were unable to take him home, but that he would be placed in the nearest and best nursing home that Medicare can buy. The daughters smiled politely and said they would inform him. Much to the social worker's surprise, the patient knew nothing about nursing home placement when she approached him three days later with the details of awaiting facility. The following day, the social worker met the daughters, again confirming the situation that home care would be impossible for them and that nursing home placement was the only viable alternative. She asked why they had not all had an "open" family discussion about the matter so that the social worker could finish making the arrangements.

Although the daughters appeared to agree, this round of events was to repeat itself twice more in three days, at which point the social worker notified the medical ward team that the arrangements were made for NT to be transferred to the nursing home, but that he refused placement, saying "I am going home; my daughters will take care of me." In a state of thorough frustration, the social worker resigned from the case.

The patient's physician met with the daughters and extended family and reaffirmed his previous understanding that the family desired around-the-clock, hospice-type institutional care for their father. The daughters appeared embarrassed by this initial public discussion and asked to speak with the physician in private. When the three were alone, the elder daughter asked the physician if he would tell their father that "the hospital wants him to go to the nursing home." The physician was dumbfounded by this request and, in turn, refused "to arm-twist the patient into accepting placement," when the elder believed that arrangements at home were already made for him.

The physician and social worker were unaware of the powerful cultural issues at stake in the Pilipino family. Elders of Asian families expect to be taken care of by their young; in fact, filial duty is considered a religious mandate as well as a social obligation. To be unable to care for one's own elders would be a "loss of face" for the children, who would be admitting publicly to moral and material inadequacy, bringing shame upon themselves and their parents. Abandoning elderly persons to the care of institutions is universally deplored, and criticism of the "dumping" family may be related to (1) negative views of institutions, which conjure earlier images of asylums and poorhouses, and resulting from modern-day scandals of neglect and profiteering in nursing homes; (2) fear of escalating costs for long-term care, believing home and family care to be the cheaper alternative, and (3) guilt of intensifying the many social and psychological losses already incurred by the aged in the aging process.[28]

Direct confrontation appears not be a sanctioned style of interaction in the Pilipino community, whereas it may be a highly valued one in the American culture in general, and in its medical subculture. The use of go-betweens, in this case the physician and hospital, would lift the onus of decision-making off the shoulders and conscience of the family. The wrath and indignation of the father could then be unleashed on the medical establishment whose reputation had already been damaged publicly and, in this way, nursing home placement would come to be accepted with minimal loss of personal and family pride.

Ultimately, the house-staff physician, functioning as a scapegoat, complied with the family's request, unwittingly colluding with the family to achieve their

purposeful ends, with the result that he felt he had somehow been violated or duped.

Discussion. The physician was actually faced with having to choose between two ethical principles: the first, to keep intact the patient's social support structure that might have ruptured had NT been confronted with the fact that his family desired him to go to the institution; the elder's humiliation, anger and withdrawal might have completely prevented the family from supporting him in other genuine ways, such as meeting his emotional and psychological needs. The second ethical principle was for the physician to be true to his own cultural values of honesty and disclosure to patients. Had he understood the implications of his or the family's actions in maintaining the Pilipino cultural norms, he might have been able to participate not with a sense of duplicity, but with one of compromise for the benefit of the patient and his family's relationship with him.

The uneasy "all's well that ends well" outcome of this case, of crossed purposes somehow achieving congruent ends without the persons involved actually making connection with one another, is, as most would agree, antithetical to a therapeutic relationship. It is difficult to say to what degree both physician and family could have acknowledged their vast cultural differences and negotiated mutually comfortable terms of resolution.

Summary

The aging process is composed of innumerable themes that may by turns be the predominant dynamic in a given situation. Due to acute catastrophic illness or to chronic progressive infirmity, the elderly are thrust into contact with health care systems of their society; this event seems to exempt no one, regardless of culture.[29]

As in all healthy relationships, a shared responsibility is essential to achieving mutual satisfaction. Both physicians and patients in the therapeutic encounter can enhance their communication and their compassion for one another by acknowledging cultural differences and by an increased willingness to interpret motives and behavior within a native context.[30] To proceed otherwise risks perpetuating the present hostilities of cultural conflicts escalated by arrogance and mistrust.

The experiences of ethnic elders reflect their desire to participate in a foreboding, culturally dissimilar health care system; it is their evident spirit of cooperation that compels me to personally and professionally deepen the meaning of the final spoken vow: "The health of my patient will be my first consideration."[1]

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Culture and Disability Behavior

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A substantial amount of literature suggests that illness behavior in the United States is a product of a patient's core culture; equally credible findings do not support this contention. Most students and graduates in the health care professions believe that illness and disability behavior are affected by a patient's culture, but they are hard put to find convincing examples of that relationship. In experience with medical students studying the social and cultural bases of illness behavior, with patients who are disabled and with persons who claim disability in the absence of physical disease or disabling psychopathology, I observed no deviant disability behavior that was typical for the members of any cultural group, and no behavior was displayed by the members of one cultural group that was not seen in members of other cultural groups. No cultural stereotypes were upheld. I did find evidence that disability behavior is influenced by personality factors, social situations and the gains derived from the disability status. Evolving concepts of "entitlement," which are closely related to socioeconomic status, also have a significant influence. The impact of feedback from others in a person's many social and medical subcultures is a more crucial determinant of illness and disability behavior, except in those for whom illness and disability behavior is determined by the limitations imposed by the disease or by a personality structure resistant to cultural expectations and social feedback.

Cultural norms and values might be expected to influence a person's disability behavior as they do one's reactions to illness and injury, but the precise nature of this influence is difficult to document. My observations about the relationship between culture and disability behavior in such a multicultural society as the United States are based on a detailed analysis of more than 2,000 persons claiming work-related disability and on a review of the pertinent literature.

Each person at birth becomes a member of a social group and thus becomes embedded in the culture of that group. Although the conceptual distinctions between "culture" and "society" are difficult to make, considering them as separate, though interdependent, phenomena is useful. Geertz notes:

> One of the ways . . . of making the distinction between culture and social system is to see the former as an ordered system of meaning and symbols in terms of which social interaction takes place; and to see the latter as the pattern of social interaction itself. On the one level is the framework of beliefs, expressive symbols, and values in terms of which individuals define their world, express their feelings, and make their judgments; on the other is the ongoing process of interactive behavior, whose persistent forms we call social structure. Culture is the fabric of meaning in terms of which human beings interpret their experience and guide their action; social structure is the form that action takes, the actually existing network of social relations.[1(pp33-34)]

Disability behavior is that subset of illness behavior exhibited when patients inform us, verbally and nonverbally, that because of the effects of illness or injury they are incapable of doing what they formerly could do. Disability behavior is *communication;* whether by word or wince, patients indicate what they cannot do: bend, lift, walk, sit, get up, pursue hobbies, exercise, have sexual intercourse or work. The form and style of this communication will vary with a person's resources. Those who lack, or believe they lack, the ability to express themselves fluently will use body language to convey the messages they want others to receive, and those whose style of interaction is histrionic, exaggerating or understated will exhibit disability behavior in their usual styles.

Because disability behavior is communication about

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a universal phenomenon—that is, illness and its functional consequences—we would expect that a patient's culture would affect, if not determine, the style, content and sequence of the messages.

Cultural factors influence the perception, classification, process of labeling, explanation and experienced meaning of symptoms and the course, decisions regarding and treatment of sickness. All societies have culturally specific theories about how and why people become ill and what being ill implies about them. The significance a symptom or illness behavior has will be linked to a society's values via its "network of meanings."[2]

Illness occurs in all cultures and forces the temporary disruption of regular patterns of social interaction and performance of role-related responsibilities. All societies, therefore, need to have certain general expectations or norms about what is appropriate behavior during illness and recovery and what seems to be a reasonable duration of exemption from usual family and work responsibilities.[3,4] Claims of continuing disability unsupported by objective physical and mental findings and demands to be supported by Workers' Compensation or Social Security benefits, then, may be considered "deviant" in terms of American cultural valuation of the "work ethic," autonomy and independent achievement.

Over the years a substantial amount of sociologic and anthropologic literature has accumulated attesting to the effects of social and cultural factors on illness and disability behavior.

Influence of Sociocultural Factors on Illness Behavior

Hinkle and Wolff[5] and Shuval and Antonovsky[6] have noted that illness is associated with a total way of life and that vulnerability is greater in groups under stress by reason of marginality, isolation, geographic or social mobility or inability to fill role expectations; changing, discontinuous or ambiguous role structure; inadequate social support, status inconsistency, blocked aspirations or inconsistency of or uncertainty about outcome of personal effort, and rapid social change.

The "folk" type of social structure prevalent in developing countries may also be found among some groups and subcultures living in highly industrialized societies.[7,8] Classifying social groups in New York into "cosmopolitan" and "parochial," Suchman,[9] for example, found that the latter, in which members belonged to closely knit ethnocentric and traditional communities and had strong friendship and family ties, tended to have a nonscientific orientation toward health, poor factual knowledge about disease, distrust of impersonal medical care and a strong dependence on their own group when ill. Both ethnicity and social class were independently related to social organization and thereby to illness behavior. Once social class and "parochial cosmopolitanism" were controlled, however, ethnic differences decreased greatly in importance.

Other studies by Zola,[10,11] Zborowski,[12] Segall[13] and Twaddle[14,15] have found ethnic differences in illness behavior among Italians, Irish, Jews and white Anglo-Saxons in New York and New England. Briefly, their studies showed that Italians tended to seek medical aid following an interpersonal crisis, rather than a change in symptoms, were more emotional in their presentation of diffuse symptoms and were less cooperative than other groups in following a prescribed regimen. The Irish and white Anglo-Saxons were more stoic, more resistant to seeking aid, more concerned about interference with their physical functioning and resisted dependency accompanying adoption of the "sick role." Whereas Jewish patients also tended to exaggerate pain sensations, they were more concerned about their implications than their relief and were more cooperative in following a physician's recommendations. White Anglo-Saxons and Irish were more eager participants in physical, but not occupational, therapy, and Jews were less concerned about physical disability as long as their intellect was intact.

In contrast to these older studies, Flannery and coworkers[16] more recently found no significant difference in pain response to episiotomy among third-generation black, Italian, Irish, Jewish and white Anglo-Saxon women when the level of education was controlled for. They suggest that the ethnic differences noted in other studies may have been due to differing levels of education among the groups and to lack of acculturation among immigrants and first-generation stock. They also point out that cultural stereotypes of health care providers may result in a perceived conformity to expectations.

Differing levels of education and cultural differences may be reflected in the widely noted tendency of certain groups to somatize their emotional distress.[17-20] Presentation of physical rather than psychologic symptoms may be related to beliefs about the causes of illness, about what a physician is for and what manifestations of illness are acceptable to a patient.[21]

In particular, both education and culture influence the language in which distress is communicated, since each culture develops a rich vocabulary around the issues that are especially important at a given time. Many subgroups have few or no words to describe psychologic distress and view expressions of bodily complaint as a natural part of the ongoing social fabric of their community. Ludwig[22] has observed, for example, that the uneducated, socially isolated persons in Appalachia combine a wide variety of nonspecific somatic and psychiatric complaints under the rubric of "nerves."

Drawing firm conclusions about the effects of culture on the above manifestations of illness behavior as documented in the literature is difficult. Evidence regarding the role of culture is conflicting. The studies are not of comparable groups in terms of education and class and were carried out in the 1950s and 1960s in Eastern urban areas where groups of immigrants still clustered together. Studies with the same ethnic groups would be impossible to replicate in 1983 due to many

forces, including population shifts, social mobility and the homogenizing effects of the mass media.

Illness behavior that affects how people perceive and interpret symptoms and why they go to a doctor—that is, "rational" illness behavior—needs to be distinguished from the "crazy" illness behavior observed in mass psychogenic illness. Mass psychogenic illness, or epidemic hysteria, is a cross-cultural phenomenon,[23] though its specific form varies according to the cultural setting. Much historical evidence supports the fact that these epidemics have been associated with cultural and social upheaval of root beliefs and value systems such as occurred during the Middle Ages in Europe and more recently during the Industrial Revolution and westernization of third-world areas such as Africa and Asia. Many authors have noted that victims of social discrimination such as the poorly educated lower classes—and within them women and children—have been commonly involved in outbreaks of mass psychogenic illness in these climates of political, religious and social unrest.[24,25] In industrialized societies, mass psychogenic illness characteristically occurs in populations of segregated women—in girls' schools, convents and among female factory workers—who are under stress in unpleasant environments.[26,27]

My own data are based on two sets of experiences. The first stems from impressions I gained from five years of teaching a first-year medical school course, Social and Cultural Bases of Illness Behavior, and the second is based on data I gathered while studying the health, illness and disability behavior of more than 2,000 persons whose claims that they were or had been disabled were being challenged, in whole or in part.

Medical Students' Attitudes

For the past six years, a course in the social and cultural bases of illness behavior has been required for first-year medical students at the University of California, San Francisco, School of Medicine. Because it is required, most students attend, and they differ from those in elective courses in including those with no special interest in social and cultural matters as well as those who would have elected to attend such a course. The format of the course has evolved over the years and each year the students evaluate the various components. In addition, they are asked to complete a learning survey, the equivalent of a final examination, from which one can not only determine what elements of the course had impressed them, but can also infer attitudes and beliefs about the impact of social and cultural forces on human behavior.

These data have indicated that the medical students believe that members of different ethnic and cultural groups have different beliefs about the causes, prevention and treatment of illness. However, they have not been satisfied that the patients who were presented to them—members of different ethnic, racial and social groups—exemplify those differences. Each year they suggest that other persons of the same ethnic or racial groups be presented, and the following year's students in turn find the samples unrepresentative. Lecturers who are themselves members of the same ethnic groups under discussion are sometimes rejected by students of the same ethnic group who suggest these lecturers are presenting stereotypes instead of a true picture. Students react similarly to literature on the subject, both to papers by professionals who are themselves members of the ethnic groups they are describing and those by recognized authorities in the fields of anthropology and sociology.

Based on this experience, I conclude that medical students of all ethnic backgrounds believe that members of different cultural groups do behave differently in thinking about and displaying illness and disability behavior, but that they are hard put to find satisfying examples of those differences and complain that the persons shown them are unrepresentative. We must consider that at the microcosmic level of an individual patient, as opposed to macrocosmic ethnic groups, there are no classic prototypes of the effects of culture on health and illness behavior.

Experience With Disabled Persons

In evaluating persons claiming disability, I conducted from one to four psychiatric examinations of these patients, each segment lasting two to three hours. In the process. a full medical and social history was taken. I reviewed medical records subpoenaed from attorneys, with many records dating back to childhood. Frequently these records included completed multiphasic health questionnaires as part of a "routine" checkup in the absence of acute physical or mental illness. Comparing complaints of illness or disability was relatively easy because they were abstracted by computer and listed at the end of a printout. Additional records reviewed consisted of work performance evaluations, reports of background investigations, discussions with co-workers and superiors and depositions. In instances where malingering was suspected, sub-rosa investigations with hidden cameras were made by insurance companies and films were shown to me after I had completed my examination and report or at the time of an administrative law hearing.

Additional data came from participation in the appeals process of the Social Security Administration. In that capacity, I did not examine applicants but reviewed conflicting written opinions from psychiatrists and psychologists and then, in the presence of the applicant, advised the administrative law judge as to the level of psychiatric disability of the applicant seeking Social Security Disability or Supplemental Security Income payments.

Further data came from the hundreds of patients I examined as a consultant to other physicians, industrial organizations and retirement boards reviewing applications for disability retirement.

Persons came from many ethnic groups and all parts of the world. They included recent immigrants from Arab countries, Polynesia, Iran, Latin America and Europe, as well as the "old Americans" whose families

had come west during the early or more recent migrations. They included skilled and unskilled urban workers, farm workers and persons working in mines 100 miles from the nearest city. Most came from lower work skill and pay levels, but a number were police chiefs, physicians, high-level administrators, university professors or self-employed.

Disability Behavior

The behavior I will describe was observed directly in the office and while watching persons interact with family and friends, was noted by co-workers and family members and was recorded in school, work or military reports or on films.

As noted, both verbal and nonverbal disability is designed to communicate that someone cannot do what they did formerly. In words, they would state that they could not do it because of pain, weakness or even paralysis—"I can't open a jar and it falls out of my hand while I'm holding it." They would complain of lack of stamina—"I can walk but I'm exhausted after a block." They said that a loss of sensation in arms or legs inhibited function. The most common complaint was that the movements necessary for performing normal tasks brought on pain or that chronic pain itself made the movements intolerable.

Disability was communicated nonverbally by stiffness or flaccidity of body parts, groans or grimaces when moving or motionless and by asking for a firmer or higher chair than the one offered. It was displayed dramatically when a person requested to lie on the floor during the interview or to maintain a position on one knee like a runner awaiting the starting gun. Some fell when entering the office and some used the wall for support. They demonstrated numbness by pinching themselves or offered to show local anesthesia by applying a lighted cigarette to the unfeeling area.

Some communicated disability by being late, explaining that they were unable to find the office because of mental confusion or because of physical discomfort that slowed their preparation or required them to stop frequently en route to get out of the car and move about. Others indicated they could not have come alone. Crutches, canes, walkers and wheelchairs were all symbols of disability, and some persons arrived by ambulance and were wheeled to the office on a gurney.

Normal Versus Deviant Disability Behavior

In all circumstances, an examiner must consider the possibility that disability behavior is factitious or deviant (or both), especially when such behavior is accompanied by evident gains for the person. Because disability behavior is communication, an examiner needs to ask if a patient is being truthful; because it is a statement of function, an examiner needs to consider the possibility of a conversion disorder. None of the displays of disability described above are considered "deviant" if justified by the diagnosis of an underlying physical or mental disorder or disease process. In the following discussion I will use the term "deviant disability behavior" to indicate that which occurs in the absence of identified disease.

One way of determining the validity of disability behavior is to note whether or not it is consistent across different contexts. Behavior may be manifested differently depending on the location of a patient, the persons present and the reason for being there. Persons who state they are disabled not infrequently behave differently when they are in a physician's waiting room or office alone than when a friend or relative is present and when walking across the parking lot than when entering the office. They behave differently when they are with other disabled people on a rehabilitation unit or in a physical therapy area than with physicians or family, or both.

Disability behavior is considered deviant when it is not explained by the presence of disease, when it is inconsistent, when it is different in different contexts and when it seems designed to "get" something—care and attention from family, escape from a sense of failure at home or work, revenge against an employer or financial support from the government or other agencies.

A collection of more than 2,000 cases has built-in controls for comparison of race, culture, socioeconomic status, age and gender. Ample data from this experience indicate that there are determinants of deviant disability behavior that do not depend on cultural or socioeconomic status. Early childhood experiences of illness and others' reactions to it strongly affect adult disability behavior. Therefore, explaining subtle differences in behavior that result from differences in culture or social group is problematic; studying examples of extreme and clearly deviant disability behavior is easier.

Clearly Deviant Disability Behavior

Persons who exhibit behavior usually associated with extreme illness and disability are found in all medical practices. Not surprisingly, they are encountered frequently in a group of patients selected for referral because their medical findings were inconsistent with their claims of disability or were inconclusive. Deviant disability behavior does not emanate from a physical or emotional illness over which a person has no control, but instead is specifically intended to impress an examiner with the severity of disability so that the examiner and others will react in what that person considers a manner favorable to him or her.

Disability deviant to an extreme is seen when someone has so exaggerated and magnified their presentation that an experienced examiner can determine even before completing an examination that the patient's behavior does not conform to any known physical or mental disorder. Those suffering from depression, anxiety or hypochondriacal disorders, then, that might cause them to believe they have a serious injury or illness and because of which they are disabled are *not* considered, by this definition, to be displaying deviant disability behavior.

In considering the role of culture in disability be-

havior, we could reasonably assume that extremes of disability behavior—clearly deviant disability behavior —would more likely carry markers identifying its cultural origin than would behavior determined by evident physical or mental impairment.

When attempting to test the hypothesis that culture or any class differences played a major role in shaping the disability behavior of the claimants I was examining, I asked the following questions:

- Was the disability behavior that had been labeled "deviant" typical of the disability behavior of other members of the same culture or class?
- Did members of other cultures and classes display the same behavior?
- Was this behavior unique in the sense that none of the other subjects displayed similar behavior?

The patients in my sample claimed that they had been disabled for at least a year (and one as long as 39 years). Multiple reports were reviewed and multiple, detailed psychiatric examinations were made of this population. Because of my background in anthropology, I was prepared to find cultural explanations for the observed differences in disability behavior. After seeing my first 50 cases, I was convinced that a patient's culture significantly affected disability behavior, but after 2,000 cases, I was no longer convinced because by then I was asking the above specific questions of the data.

Results

At a conservative estimate, at least half of the persons I examined displayed deviant disability behavior.

No deviant disability behavior was observed that was typical for the members of any cultural group.

No behavior was displayed by members of one cultural group that was not seen in members of other cultural groups.

No cultural stereotypes were upheld. Examples of unique and extreme disability behavior were seen as frequently among persons of northern European ancestry as among those of Oriental, Mediterranean or other racial and ethnic backgrounds.

Discussion

Cultural factors do affect illness and disability, just as they affect mourning behavior, courting behavior and the meanings attached to religion and to work. Cultural factors are not enough, however, to explain the differences in disability behavior. Determining the cultural origins of individual disability behavior would be easier if persons had recently immigrated from a society with a relatively homogeneous culture that had recently been studied. But we live in McLuhan's "global village"; the rapidity of cultural change even in remote areas has been well documented, and acculturation is unquestionably even more rapid among immigrants to the United States.

Examples abound of persons leaving their core culture or of breaking away from a homogeneous cultural group whose precepts they found coercive and restrictive. The rules of any group are obeyed in part because members have internalized them and in part because of the balance between rewards and dissatisfactions that come from obeying them. The dissatisfaction increases as a person, by either independent discovery or contact with other cultural groups, learns other ways of behaving and of doing things that promise greater rewards. The tendency to depart from the practices of a core group increases if the new group is regarded as more advanced and if its practices seem more advantageous.

Most members of American subcultures—and, for many, several generations of their families—have been exposed to the greater American cultural scene for many years. Therefore, we should not be surprised that the prescribed practices for illness and disability behavior in these subcultures have changed, just as they have for sexual behavior and intergenerational relationships, and that finding the traces of the old culture in these behaviors may be more difficult than discovering the impact of the new one. Culture, then, is not a monolithic force that operates inexorably and uniformly on all segments of society. Other social and psychologic factors operating concurrently affect the course of disability behavior.

Feedback and Disability Behavior

Whereas illness and disability behavior depend in part on the presence of disease or its sequelae that produce physical impairment and in part on styles of communication or behavior patterns that are inherited or learned, they also are considerably influenced by the feedback of others to this behavior.

Disease, for example, determines a substantial part of the illness and disability behavior in patients with angina pectoris or myocardial infarction. These patients cannot ignore the pain, even though they may choose to try to conceal it. A patient with claudication must stop and rest; the physical impairment determines the patient's disease behavior.

In the absence of disease, we can assume that differences in illness behavior are partly determined by a person's personality and by sociocultural forces. However, we still need to explain the variations that occur with the passage of time or with changes in context, such as when a person is with a physician who is evaluating the disability or with a spouse who may resent having to do the patient's chores or with friends in recreational settings.

To understand these variations, we must consider that illness and disability behavior are partly determined by verbal and nonverbal feedback from persons interacting with a patient and that the cues patients pick up help shape their behavior. A patient's response depends on his or her evaluation of the validity of the feedback, of the person responding on a judgment about the intentions or motives and on the patient's receptivity to feedback generally.

Some persons are resistant to and distort feedback.

Those who are depressed have a pessimistic outlook and schizophrenic patients' reality is severely distorted and distorts feedback. Hypochondriacal patients are convinced something is wrong with their health despite reassurances to the contrary. Persons with a hysterical character are acting out a script on a nonverbal level, and their numerous somatic symptoms are impervious to authoritative feedback. Malingerers and those with factitious disorders, of course, have their own agenda, and their illness behavior is calculated to accomplish certain ends. Persons with an organic mental impairment also have difficulty in responding to feedback.

On the other end of the spectrum are those who are notably responsive to feedback, such as the hypersuggestible and those particularly swayed by authoritarian or charismatic persons. The devotees of faith healers or purveyors of quack cancer cures are overly responsive to feedback, as are those easily hypnotized. Some of these persons may actually be harmed when they believe nothing is wrong or that they are well when in fact a serious and treatable health condition exists.

Because of different relationships that in themselves partly structure reactions, the feedback one receives is never absolutely "pure." Certain relationships are inherently unequal, such as between a parent and child or a physician and patient, and the response to feedback in those situations will be different from feedback from a spouse or close friend.

In relatively homogeneous cultures feedback is "purer" in the sense that it is more uniform. As societies become more complex, however, and as more people of differing backgrounds and with different roles are called upon to interact, there are more conflicting feedback channels that a patient must evaluate and respond to.

These messages to which persons selectively respond depend in part on their beliefs, which determine what is "possible" in their world view as well as structure their interpretation of events. Persons who believe they have had a curse placed on them will interpret physical symptoms differently from those who believe they have the flu caused by a virus that is "going around." An unusual odor in a workplace will be responded to differently by someone working in a chemical plant and someone in a toy store. Those who believe they are "allergic to everything" will select feedback that supports this belief and will ignore all other.[28] Persons, therefore, tend to respond to feedback that supports their expectations based on beliefs and frames of reference.

Although culture provides the general background against which disability behavior is displayed, the more immediate determinant of the form of its expression, aside from actual physical impairment, is the feedback from others in a person's many subcultures, social and medical, and each feedback experience affects that behavior further except in those whose illness and disability behavior is determined by the limitations imposed by disease, or by a personality structure resistant to cultural expectations and to social feedback.

Public Policy and Disability Behavior

All agree that disability behavior is affected by the benefits that are available. That there even exists a means for providing a decent standard of living for disabled persons in this culture is affected both by humanitarian motives and by the high level of economic affluence. Productivity, especially during a time of peace, is not a problem, so lack of work contribution by disabled persons is not dysfunctional for the economy.[28-30]

The number of government or privately supported disabled persons has risen dramatically and a "problem population" now exists.[31] Disability benefits provide a channel by which those who cannot work, for whatever reasons, can be freed of occupational obligations.

Commenting on the influence of Social Security on this subset of illness behavior, Weijel observes that ailments of divergent origins are funneled into the system:

> . . . purely somatic diseases, psychosomatic disturbances, social inadequacy, the onset of aging, the fear of unemployment—everything that threatens individual and social well-being. Historical development caused only sickness to be a real excuse to drop out, and all that human misery, failure, and deficiency is, therefore, drained into the medical channel.[32(p278)]

Work and Disability Behavior

Why do some persons—regardless of diagnosis—perceive themselves as disabled and take refuge in and capitalize on that disability? Deviant disability behavior following workplace injury or occupational illness is not randomly distributed, but appears to occur most commonly in the following two groups: one, the "socially disabled,"[33] often unskilled or semiskilled blue-collar workers who have never seen themselves as integral parts of their work subculture and actively reject the values, rules and customs, especially pertaining to the "work ethic." Many of these are manual laborers with unpleasant or completely routinized tasks providing marginal financial rewards. Two, the "hyperadapters"[34] are those always conscientious, responsible, hard-working persons who strongly identify with their work subcultures, but at some point become disillusioned and feel angry and resentful if employers are not appreciative enough of their efforts or act unfairly. Ford[35] describes the disability behavior in this latter group as the "Humpty Dumpty syndrome." These workers often believe they have been sabotaged by coworkers or superiors, have been harassed or passed over for promotion, that workplace nepotism has turned to their disadvantage or that their employers or a company physician failed to care for them adequately after an illness or injury. Sometimes they become depressed or "burned out" and reject the objectives and practices of their work subcultures.[36,37]

Several investigators postulate that there is in some workers a predisposition to entering the disability channel that begins before injury or illness and is grounded in a rigid personality or a fragile or negative predis-

ability self-concept or unexpressed anger and dependency needs reinforced by social or occupational stress, or both.[38-43] Persons who can define themselves as physically disabled can more easily accept their need to be taken care of or to stop working.

Entitlement

Deviant disability behavior is closely related to the notion of "entitlement"[44,45]—the feeling of individuals that they have suffered an injustice and that society owes them something—and each subgroup in our society has a different focus of entitlement. Many who have large incomes believe that they are entitled to keep all of their earnings and that the tax loopholes enabling them to avoid substantial taxation are fair. They resent legislative efforts to eliminate their "shelters" just as much as those receiving Workers' Compensation or Supplemental Security Income benefits will struggle to obtain or keep what they so firmly believe they are entitled to even in the absence of a qualifying disability.

Many persons in lower socioeconomic strata are unaware of the benefits available to them and the conditions under which they are entitled to them. Those in the so-called underclass,[46] the very poor who depend entirely on welfare, are aware of one set of benefits. Those who have worked and come from families who have never been on welfare may recall that a relative once worked for some Depression relief program like the WPA (Works Progress Administration), but they themselves may be only vaguely aware of benefits that even some members of their own group are receiving until they can no longer support themselves.

While some have suggested that some people are just awaiting any change in circumstances that will permit them to "tap in on their entitlements," my impression is that most of those who do are forced to. Once they do tap in on disability benefits, however, their living pattern is altered. Some discover that they can receive more usable income when disabled than they ever did when employed. For some, a slight drop in income is balanced by the freedom from work. Others are outraged to discover how greatly they are disadvantaged, that their income of $15,000 to $30,000 has dropped on compensation to $9,000 or less, without any reduction in their financial obligations; if they could, they would leave the disability channel.

Subcultural Mores and Disability Behavior

The culture of individuals' own groups—their subculture—comes into play and determines their attitude toward invoking entitlements, their notions of how disabled one must be to continue to receive benefits and their acceptance or rejection by other members of the group if they believe the disability is unduly prolonged, unjustified or that the person is malingering.

The blue-collar workers' "tavern subculture" is described by Kotarba[47] as providing instrumental assistance to the disabled in terms of discussions of "folk cures," how to apply for benefits and which physicians or attorneys to see and offering sympathy and sociability. This subculture, he notes, can be unsupportive of those felt to be malingering.

Co-workers are intolerant of disabled fellow workers who attempt to return to light duty and they deride those considered to be malingering, making no distinction between "conscious" and "unconscious" reasons for deviant behavior. This intolerance is manifested particularly when the workload of those not disabled is increased, but even when their workload is unchanged, they are likely to consider the lighter workload of a partially disabled person to be unfair and to complain to management if they believe the claim of disability is unjustified.

Among the persons I have examined, many were rejected outright by their own families, friends, former co-workers and communities when their claims were considered unjustified and deviant. The cultural values of one's group, particularly one's family, rather than the ethnic or racial group with which one is associated in the census, determine the criteria for acceptability of disability behavior and the judgment of whether or not a disabled person is entitled to benefits.

Many years ago a noted anthropologist[48] commented that "culture walks on two feet," suggesting that we do not see culture as such, but rather human behavior and products. Just as we do grave injustices to people when we permit racial or ethnic stereotypes to guide our judgments and treatment of them, so too in medicine can we be unjust in accepting cultural stereotypes of illness and disability behavior.

Within broad cultural communities, there are almost infinite differences in health and illness behavior. Whether the medical effort is prevention or treatment, a health care professional must consider the impact not only of a person's culture but also of the other biologic, psychologic and social forces that make a person unique with the illness and disability behavior that person exhibits. Judging the presence of cultural influences in a single patient's illness and disability behavior is ultimately a function of the eye of the beholder, and the literature reports no "double blind" test that safeguards against the biases involved in relating culture to disability behavior.

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Aspects of Medical Care of Soviet Jewish Emigrés

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Soviet Jewish emigrés are a recently arrived refugee group in San Francisco and in other cities in the United States. They have frequently been perceived as a demanding and complaining population, particularly the elderly, often chronically ill members. These behaviors can also be seen as positive survival mechanisms that have evolved in response to the Soviet health care system and cultural background. An understanding of that background and system, together with time, greatly improves the interaction between Soviet Jewish patients and American physicians.

Since 1974 Mount Zion Hospital and Medical Center in San Francisco has served as one of the main health care providers for the Soviet Jewish emigré population in San Francisco. About 5,000 recently arrived Russian Jews live in the Bay Area. Many are related because one of the conditions for immigration to the United States is that an emigré move to a locale where sponsors (most frequently relatives) are. Close ties exist within the community because of familial ties and cultural experiences, as well as a common language. With the assistance of the Jewish Welfare Federation, Mount Zion has been able to provide specialized services such as Russian translators and has served as a main health care provider for this population, especially the elderly. We have found the elderly population particularly challenging. They suffer from all the illnesses that commonly affect the old—diabetes, heart disease and arthritis. In addition, many appear to emphasize their symptoms out of proportion to disease activity at any given time. Many of these patients are extremely depressed, their unhappiness being expressed in somatization. Over the years a pattern of health care behavior has become apparent that has frequently been perceived as difficult or maladaptive by resident physicians who have cared for these patients. The Soviet Jews do not fit the American model of a "good" patient. However, as we explore the sociocultural background of these patients, particularly the health care system in the Soviet Union,[1-6] these behaviors emerge as highly adaptive survival mechanisms.

The Russian Jew who emigrates from the Soviet Union has been identified as a member of a stigmatized group. Frequently the desire to leave Russia is a result of religious conviction (often more an expression of cultural identification than religious observance) coupled with a desire for economic improvement. Jews in the Soviet Union are consistently denied more prestigious and high-paying jobs; consequently, the already difficult economic position of most Soviet citizens is worsened for them. Nevertheless, the decision to emigrate requires courage. Many years may elapse between application and permission. During this time job opportunities diminish further, educational opportunities may be curtailed and status decreases. Government or official response to problems essentially vanishes as the potential emigré becomes a "nonperson" through his or her nonsupport of the government—a nonsupport that is shown by the application to leave. With emigration, citizenship is permanently revoked and there is no possibility of return to the Soviet Union.

The Soviet government expends few resources on older, nonproductive citizens. Nursing homes as we know them do not exist; the care of the elderly is the responsibility of the family. When younger Soviet Jews receive permission to emigrate, it is frequently contingent on their taking their elderly parent(s) as well. As a result, Russians in the 70s and 80s, often chronically ill, agree for their children's sakes to leave their country. Because they themselves lack a personal motivation to emigrate, their transition to a totally new culture is particularly difficult, and significant family stress may result.

Even the younger Soviet Jewish emigrés, despite their desire to leave, are products of the Russian

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Soviet cultural background. They have always lived and worked in an authoritarian, group-oriented culture where the needs of the state routinely supersede those of the individual. Some emigrés express a desire for "freedom," yet this remains an abstraction poorly understood by members of a regimented, bureaucratic society. The day-to-day expressions of freedom in the United States frequently become a major source of anxiety and disorientation for a new emigré. Although the Soviet Union may appear to us a regimented and controlled society with a lower standard of living than our own, the expectation of state-provided basic economic security is universal. As one Russian doctor states: "As a student I was taught the four basic socialist rights—the right to work, the right to a free education, the right to free medical care and the right to a pension following retirement."[7(p101)] By contrast, the general perception of American medical care is that of a technologically advanced but money-oriented system available only to the rich. Many believe that "Americans have to sell their homes and cars to pay for medicine."[7(p113)] Thus, a general anxiety about finances in a group allowed to leave Russia with only $90 per person may focus specifically on medical care. This fear interacts with the anxiety of being thrust into a society emphasizing individual responsibilities in a country that has been routinely denigrated by the Soviet Union.

We will now turn to an examination of several cases of Russian* patients seen in our clinics and on our wards. Each case shows an instance of conflict in medical-role expectations resulting from discrepancies in cultural background between physicians and patients. The following areas of conflict are discussed in this article: timing and scheduling, patient-practitioner relationships, diagnostic testing, medicine and compliance, outpatient versus inpatient care and accuracy of reporting.

Reports of Cases

Conflicts in Timing and Scheduling

CASE 1. BF, a 72-year-old Russian woman, entered the waiting room when it opened at 8 AM and complained loudly to a nurse at 9 AM that she had not been seen yet. The nurse checked her appointment slip, noted that it was for 10 AM and explained this briefly to the patient through an interpreter. She assured her that she would be seen. At 9:30 AM BF was found in the doctors' conference room waving her appointment slip and pointing to the examining room across the hall; she was sent back to the waiting room. However, when the nurse went to put the next patient in a room, she found BF calmly settled in the vacant examination room waiting to see a doctor.

CASE 2. YG, an 84-year-old Russian man, arrived at 11 AM with his appointment slip for a history and physical examination at 8:30 AM that day. When told that he had missed his appointment and would have to reschedule, he insisted that he had an appointment. Again told to reschedule, the patient complained of severe chest pain and insisted that he must be seen that day. Because of the complaint of chest pain, he was given a drop-in appointment.

Discussion. Both BF and YG illustrate the attitude toward appointments and time that exists in the Soviet medical system. The polyclinics are open a set number of hours and physicians work a fixed shift. If all appointed patients have not been seen by the end of the shift, the physician simply leaves and the patients must return the next day. Schedules are rarely adhered to and appointments are not necessarily honored. Patients who arrive very early in the polyclinic to submit their names and repeatedly remind a nurse or desk clerk of their presence stand a better chance of being seen: "The door that squeaks gets oiled." Some polyclinics routinely run so far behind schedule, however, that Russian patients with less sense of urgency about their symptoms may simply arrive late to save time. One of our Russian patients described it this way: "If you would like to be seen on time, come late. Come even later." Arriving early with frequent complaining and arriving long after the appointment time both represent effective adaptation to the Soviet system. Finally, YG's subsequent complaint of severe chest pain indicates his adaptation to our system. Mount Zion attempts to see urgent care drop-ins along with appointed patients. Nurses, however, screen all patients and reschedule those whose complaints can wait. Our Russian patients are well aware that a complaint of chest pain, particularly in an elderly patient, will insure their being seen promptly! Each time such an event occurs, we see clearly how they have been able to survive as a minority group and how that survival behavior continues here.

Conflicts in Patient-Practitioner Relationships

Physician-patient relationships in Russia are ordinarily authoritarian rather than egalitarian; such relationships rarely promote free exchange of information and open discussion. Our resident physicians complain that Russian patients often do not know what has happened to them—for example, what an operation was for. In the Soviet Union patients are often not told why an operation is done. Cancer is never a diagnosis; even resections of bulky masses are always for "premalignancy." There is *no* continuity of inpatient care and Soviet hospital physicians share virtually no information with their patients about diagnosis or prognosis. Conversely, patients, particularly inpatients, consider it presumptuous to question a physician or discuss medical issues. Demeanor and social interaction style may also create difficulties, as the following case shows.

CASE 3. An elderly Russian woman complained that while in the coronary care unit she was "assaulted" and ridiculed by three nurses. Further explanation elicited that one nurse had drawn blood, another had simply combed the patient's hair, while the third one had made the bed. The patient explained that she knew that they were making fun of her because they were smiling.

Discussion. The Russian approach to illness is very

*In the following discussion "Russian" will be used to refer to the Soviet Jewish emigrés.

serious. Illness is not something to smile about; smiling indicates that a person is not serious and is not assuming the proper responsibility for a patient's health care. Smiling is a sign of weakness as well. Strong, competent professionals will have a serious demeanor. Furthermore, in Russia smiling is an appropriate form of communication only between close friends. It is not suitable to the formal relationship between physician and patient or nurse and patient. In this setting, as indicated by the patient in case 3, a smile is interpreted as ridicule. Our morning work rounds, with groups of people clustered around the bed, all smiling at a patient, are easily misunderstood. Smiles themselves can vary as well. Apparently the American smile is viewed by Russians as more of a social grimace. A real smile is more open, warmer, lasts longer and indicates intimate friendship and trust. Even if an American smile is perceived as friendly rather than insulting, it is still not appropriate to the physician-patient relationship.

Age and dress work against the American resident physician as well. Youth is suspect; beginners are not to be trusted. Age, wisdom and experience go together and are valued more than recent knowledge and skills. The appropriate image for a physician is a large, grey- or white-haired man, preferably with a beard. Uniforms are another important prerequisite; all health personnel in the Soviet Union wear a definite uniform. With this formality of dress and appearance come the expectation of a formal and authoritarian relationship as well. We have mentioned the organized, managed nature of most aspects of Soviet life. Additionally, health is seen as a resource of the state, not as a responsibility of individual persons requiring their active decision. Because the right to free medical care is one of the four basic socialist rights, and the productivity and health of each person are a state resource, physicians are seen as government officials and authority figures. The expected relationship is a caring but paternalistic one—a patient expects to be told what to do. Not only is involvement of a patient in decisions regarding medication, tests or treatment unexpected and anxiety producing, it also indicates that a physician does not know what he or she is doing. This further increases a patient's perception of incompetence already suggested by the young age of our residents and their informal dress and smiling approach. Our resident physicians do not fit the model of "good" doctors for Russian patients any more than Russian patients fit the American model of "good" patients.

One way our Russian patients cope with their perception of inadequate American physicians is to request a specialist. Referrals are a commonly used mechanism in the Soviet Union, particularly for chronic complaints such as dizziness or atypical chest pain. The primary physician gets a breather and the patient feels that something is being done, that his or her complaints are being taken seriously. At Mount Zion specialists are more likely to be older and more appropriate-looking. This helps restore a patient's trust in an unfamiliar system.

Conflicts Over Diagnostic Testing

Russian patients request and accept specialist evaluation much more readily than diagnostic testing. In the Soviet Union referrals are an available substitute for scarce and often rudimentary technology. For example, a chest roentgenogram not infrequently requires a week's scheduling. Obtaining a radioisotope liver scan in the city of Kishinev requires five separate forms, approval of six different persons and a ten-day wait.[7(p107)] Obviously such procedures will not be attempted nor approved for trivial conditions. What is found is usually serious and a workup generally is not pursued until a patient is quite ill. This strengthens a Russian's perception of the association between tests and serious illness. Psychologically he or she is not likely to agree to testing unless significant symptoms are present. The very availability of our diagnostic tests is another hindrance. If something can be gotten readily it must not be worth very much or, worse, the only possible benefit is to the physician, who must be using them as guinea pigs. This feeling is particularly prevalent among the elderly because even fewer resources would be allotted to them in the Soviet Union, and because memories of Nazi medical experimentation on Jews are strong.

Medication and Compliance

Compliance with medicines is affected by the physician-patient relationship and by the availability of medicines. As we have discussed, inclusion of the patient in the decision-making process or in a discussion of possible side effects of drugs weakens the authoritarian structure to which a Russian patient is accustomed. Ironically, the general availability of American pharmaceuticals also decreases compliance. Medicines are not easily obtained in the Soviet Union. Supply is erratic and only a small number of drugs is available. A Russian patient is accustomed to expending a good deal of energy and ingenuity to obtain a needed drug; this very difficulty may add to the therapeutic effect. From the point of view of a Russian patient, if a medicine is so readily available that one merely walks to a pharmacy and picks it up the same day, then it cannot be very effective and the patient has little motivation to use it. Furthermore, Russian patients firmly believe that all drugs are a poison in some way. They will stop using them at the first resolution of symptoms. Medicine is less frequently prescribed in the Soviet Union, "natural" remedies being used more often. A patient with a chronic disease, such as low back pain or lung problems, hopes for a trip to a sanatorium where mineral water, mud baths and light exercise form an integral part of the treatment. These visits are for extended periods, 24 days or more, and the personal attention, so difficult to obtain in any other area of Soviet life, obviously constitutes an important part of their appeal.

One polyclinic doctor states, "I don't use many drugs, sometimes an antibiotic or mild tranquilizer. Mostly I prescribe a combination of herbs. We have some excellent herbal drugs."[7(pp101-102)] A frequently

prescribed Russian medicine in the Mount Zion clinic is tincture of valerian, eight to ten drops taken in a glass of water. Valerian is an alkaloid herb valued for its relaxant and soporific properties. Its effect, whether medicinal or placebo, appears to be powerful because few patients request anything further for symptoms of insomnia or anxiety. The use of valerian has required education on the part of our residents. Their initial reaction was to ignore such a nontechnologic and unproved preparation—even though its use seems effective in exactly those situations wherein Western medicine has shown few remedies of established, long-term benefit. Overall, our tendency to involve Russian patients in the decision-making process, explain the possible side effects of medicines and have the medicines readily available insures that they are presented in the least favorable and most prejudicial light possible to Russian patients. Their entire cultural background emphasizes the risk and negates or minimizes any likely benefit.

Outpatient Versus Inpatient Care

Perceptions of good inpatient care and patient hospital behavior are also strongly affected by Russian patients' cultural background. Health care in the Soviet Union has five separate levels. At the first level is village medicine provided by a *feldsher* (physician assistant). This is unsophisticated, extremely basic care. Misdiagnosis is common; mortality is high for all diseases and particularly for infants. At the next level is outpatient, polyclinic care. This is provided in a city, but is completely separate from hospital care. Polyclinic physicians never provide inpatient care and do not continue caring for their patients who enter hospital. Outpatient care is perceived as of lower quality than hospital treatment. At the third level is the nonteaching hospital. Because equipment and resources are extremely limited, patients are assigned to hospitals according to diagnosis; consequently, the location, even in a city, may be a great distance from a patient's home. The fourth level of care is the academic teaching hospital, which provides patient care within the context of teaching and research needs. This is the highest level of care available to a nonparty member (about 9% of Soviet citizens are members of the Communist Party). Patients are referred to teaching hospitals on the basis of the interest of their cases. Because this is the best care that most people can obtain, many patients exaggerate or prolong symptoms in an effort to be referred as "interesting cases." If they are not entitled to teaching care on the basis of diagnosis, then they are required to pay for it. Finally, the fifth level of care is that provided to high officials and party members by a Department of the Ministry of Health. This care is considered to be excellent by any standard, but it is available to only a small percentage of the population.

This organization of the Soviet health care system affects a Russian patient's perception of care in the United States. For example, when patients are admitted from our clinic and receive ward care from physicians who have cared for them as outpatients, this seems to them a lower quality of care.

The most common treatment in the Soviet Union is simple bed rest. Patients are admitted to hospital for uncomplicated gastritis, pneumonia or influenza that American physicians would treat at home. Part of this reflects the overcrowding of Soviet living space. With an entire family quartered in one or two rooms there is no space for a sick person to remain in bed. Conversely, quality of care is judged by a Russian patient as length of time in bed. *Minimum* length of stays are allotted for each illness. For example, an uncomplicated appendectomy requires a ten-day hospital stay. A female Russian patient complained about the quality of her friend's care at Mount Zion:

> A friend of mine had her gallbladder taken out. After two days they already wanted her to walk and move. After just two weeks they thought she should go home. I remember *my* gallbladder operation in Russia. I got peritonitis and stayed in bed three months.

Our concept of short hospital stays and utilization review simply means poor care to a Russian. Hospital use in the Soviet Union reflects this: One of every four Russians is admitted to hospital each year (one of seven in the United States), average stay per person per year is 2.8 days (compared with 1.2 in the United States) and the mean hospital stay is 15 days (compared with five days in the United States).[7]

Just as we have seen that demanding, complaining behavior by a Russian clinic patient represents an effective coping mechanism adapted to the Soviet system, we can see that this behavior in hospital also reflects the Soviet background. First, although all medical care, including hospital costs, is allegedly free, large areas of ambiguity exist in this system. Salaries for health care workers in the Soviet Union are so low that some sort of tip or auxiliary payment is expected from patients. Nurses may get three rubles for changing sheets (every ten days); extra money is offered and accepted for routine nursing care—such as baths or prompt delivery of pain medication. Perhaps even more important, unofficial payments are an important entry mechanism into academic hospitals. Russian patients are genuinely surprised when bribery or manipulation is negatively viewed here; it is an expected and necessary part of the system to which they are accustomed. Furthermore, the system of special treatment for a fee explains part of their suspicion regarding our quality of care. Yes, we are providing care, but it is difficult for them to believe that we are providing our *best* care: after all, no gift has changed hands.

Accuracy of Reporting

History taking and follow-up of symptoms is complicated by a tendency to exaggerate symptoms to obtain optimal care. Patients' reports are sometimes unreliable from another viewpoint as well. Culturally, perhaps as an adaptation to scarce health care resources, a Russian patient does not accept recovery quickly. Negative feelings, however, are expressed easily and completely. We must rely on objective data,

not history, for an accurate assessment of stage of recovery because for a long period of time a Russian patient will only feel "not good." A patient will emphasize any symptoms to justify remaining in bed because bed rest is the index of good care and recovery. Perhaps the overall Russian attitude toward health and symptoms is best expressed by an old Russian woman who always went to a sanatorium on her vacation: "After all, you are always sick with something."[7(p251)]

CASE 4. FS, a 78-year-old woman, emigrated from the Soviet Union in 1979 and was diagnosed as having metastatic breast carcinoma and tuberculosis. She was a fragile and chronically ill patient who refused workup of her pleural effusions until she could no longer walk across the room. Although her tuberculosis had been cured, she still suffered from severe arthritis and one-block dyspnea and she was legally blind. Nonetheless, when asked on her most recent clinic visit (June 1983) how she was feeling, she answered in English "fine." When her clinic physician commented that she was the only one of her Russian patients who ever said "fine," FS explained through an interpreter that she had learned that "fine" was what one should answer when an American doctor asked how you were feeling.

Cultural Accommodation in Case Management

The experience of FS (case 4) poignantly shows the profound differences between the expectations of patient and physician in the two health care systems. Our Russian patients expect to complain to obtain needed attention and service. American physicians need their patients to say they are fine. It also shows the adaptation that occurs with time. When FS first came to the United States, she followed a pattern of refusing workup until severe symptoms were present. Now she has learned to say "fine" and credits her clinic physician with saving her life. She takes her complex regimen of medicines (glaucoma medicine, tamoxifen citrate and diuretics) regularly and brings all her bottles with her to each visit. Despite a Russian taboo regarding cancer, she told a translator that she thinks she has cancer, but also said that she did not want to discuss this with a physician. On one visit she repeatedly stated her readiness to die; yet on the same visit, when asked specifically about her symptoms, said "Thank God things are not any worse."

FS is a survivor who, despite age and illness, is adapting to her American environment. She is perceptive, realistic and has much to teach her physicians about the gifts and limitations of medicine. Despite the smiles and informality of her female American physician, FS has learned to recognize the attentiveness and goodwill that underlies it. Indeed, it is their personal relationship, evolving over time, that has transcended the cultural barriers. Her physician has learned, too; she no longer tries to discuss FS's diagnosis of cancer (all lung problems are attributed to tuberculosis). She recognizes FS's anxiety about tests and orders them only when treatment would be affected. In short, the physician has curbed some of her own anxiety about chronic illness—an anxiety sometimes manifested in a desire to name things that one cannot change. She has come to understand one positive aspect of the technologic limitations of Soviet medicine. This was expressed by a Russian doctor after visiting an American academic intensive care unit: "That is the difference. In America you think medicine can do everything. In Russia we understand its limits."[7(p350)]

Relationship and understanding have greatly improved the interactions between our residents and their Russian patients. Complaints are far fewer on both sides. Regular patients, even when difficult, begin to be regarded with affection and even admiration—for the inventiveness of their symptoms and their survival behavior! As residents have learned about the background of these patients, their frustration with patient behavior has greatly decreased, interrupting a negative spiral. The residents are also more careful in how they present themselves, as well as in interpreting behavior. They are more aware of where and why misunderstandings occur and are willing to work with a patient over a long period of time.

CASE 5. FV, a 64-year-old woman, was noted by her physician to have a breast mass in 1981. Despite his discussions of risk and the possibility of cancer, as well as highly suspicious findings on a mammogram, she refused biopsy or operation. The resident continued to see her with long regular visits and much attention. Following development of an axillary node 15 months later (six months after her husband died of colon cancer), FV agreed to an operation. Two of 25 nodes were positive and she is doing well six months after the surgical procedure. She did not agree to adjuvant chemotherapy but is regularly taking tamoxifen for her estrogen-receptor-positive tumor. When her resident left after three years of caring for (and about) her, she gave him a carved Russian chess set.

Of course any immigrant group has its own cultural background that often differs greatly from our own. The Soviet Jewish emigrés have been a particularly interesting group for us, in part because of our initial ignorance of the Soviet health care system and cultural background. It has been a fascinating experience to see demanding or complaining behavior switch from a negative to a positive value—though it can still be unpleasant!—as we have begun to understand its function in their cultural background. This has enabled us to provide care more dispassionately and in a manner more understandable to them. We have learned from one another and it is hoped that each of us has acquired a better appreciation of the interaction of human and cultural values and health care.

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The Role of a Community-Based Satellite Clinic in the Perinatal Care of Non-English-Speaking Immigrants

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In the provision of health care to non-English-speaking immigrants, cultural and linguistic barriers often deter both access to and use of needed services. This is especially true of the preventive health interventions such as perinatal care and family planning that contribute significantly to reproductive health.

Alternative approaches to overcoming barriers to care are being taken in an urban health department clinic serving as a satellite perinatal resource to a group of low-income Chinese-speaking immigrants. The clinic, with service linkages to San Francisco General Hospital Medical Center and the Health Department of San Francisco City and County, is an example of culturally appropriate comprehensive perinatal care. Such an institution has helped recent immigrants adapt to their new environment and learn to use health services effectively.

The field of international health occupies a singularly minor role in American schools of medicine and public health. Dr John Knowles, President of the Rockefeller Foundation, noted in 1976[1] that there were fewer than 10 independent departments of tropical medicine and international health in 107 US medical schools, and only 5 such departments among 18 US schools of public health. It follows that relatively few American physicians are likely to be fully acquainted with the range of health problems prevalent in recent immigrants, particularly those from developing countries. Of even greater importance from a practical standpoint is the need for awareness of the cultural barriers that hinder immigrants' access to, and effective use of, this country's diverse health care resources.

Immigration to the United States has increased since the middle 1970s, when roughly 400,000 legal immigrants entered the country each year. With the added influx of refugees, legal immigration figures in recent years have risen to between 600,000 and 800,000 a year. Illegal immigration obviously cannot be measured, but is thought to add another 100,000 to 500,000 annually. Whether of regular immigrants, refugees or "undocumented aliens," the flow of new arrivals to the United States continues unabated. Some—the economically self-sufficient, the educated with marketable skills or those with extended family support systems already established in the United States—may experience the transition to their new environment with little disruption of their lives. For most, however, the transition poses special problems of particular relevance to health providers. Most of the medical literature on immigrants, particularly that dealing with the recent influx from Indochinese countries, focuses on abnormalities that appear in screening programs or the prevalence of particular diseases brought with them. However, not only is their health often impaired by undernutrition, parasitic and other infectious diseases, or childhood histories of poor health; in addition, their poverty, their unfamiliarity with and fear of medical institutions and health interventions in the new country, and the language barrier itself make them inefficient and often reluctant consumers of health services. Many come from areas where modern scientific medicine is unavailable, and where indigenous healers and untrained traditional birth attendants were as a rule their only resource for care during illness or pregnancy. For such immigrants, the vast array of preventive and curative

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interventions to which Americans are accustomed (indeed, overdependent, according to Illich![2]) is often completely unintelligible.

These observations are neither new nor controversial; nevertheless, they assume particular importance in the field of reproductive health, in which preventive measures are especially central. We know, for example, that all societies respond to illness and trauma with culturally determined attempts to cure symptoms and restore individual and community well-being. Notions of preventing illness are universal but frequently differ conceptually and in practice from biomedical theory. It is thus not surprising that immigrant women's ideas of optimal perinatal care do not correspond to those of scientific obstetrics.

In view of the large percentage of the immigrant population that is composed of women of childbearing age and young children, it is important to design and deliver services that will ensure maximal use by these especially vulnerable groups. In this context, appropriate cross-cultural communication with immigrant patients to minimize ambiguity and enhance constructive health behavior may in many instances prove more important in its long-term effects on their health than the application of technologic interventions.

Among alternatives in the organization of care for low-income immigrants, several models are available for consideration. The common American private practice, fee-for-service model may be admirably suited to immigrants' special needs when the care is personalized, and the practitioner is linguistically compatible with the patient and has ample time to provide the extra attention required to assure informed compliance with treatment regimens. For those who are in a low-income category and dependent on Medicaid, however, the level of reimbursement to providers hardly permits the added time and energy that such care requires.

Hospital-based clinics, particularly those of large metropolitan institutions with services designed for efficiency and the convenience of providers, tend to be crowded, impersonal and bewildering. Before the clinic is even reached, physical access to services, taken for granted by most Americans, may involve seemingly innocuous but nonetheless important logistic obstacles in the form of appointment procedures, difficult public transportation connections or formidable-appearing buildings and directional signs written in an alien language. Organizational and structural barriers to obtaining clinical care such as these often compound problems of use.

A model of comprehensive care with special relevance to the reproductive health needs of immigrant women, the Maternal and Infant Care (MIC) projects, was developed as a result of the 1963 amendments to Title V of the Social Security Act[3] in an effort to reach disadvantaged segments of the population characterized by poverty and high infant mortality. Altogether, 56 such projects had been created by 1974, with 75% of the costs provided by the federal government. The maternal and infant care projects, eclectic in character and designed as demonstrations, were generally successful in promoting earlier prenatal care, improved nutrition and better compliance with a range of services delivered by multidisciplinary teams, and contributed to a reduction in infant mortality and morbidity. Their comprehensiveness derived from the augmentation of routine prenatal care with special outreach activity for early enrollment, social services, health education, nutrition counseling and in some instances special adjuncts such as dental care. They have gradually been absorbed into ongoing delivery systems, but their distinguishing features of comprehensiveness, decentralization and care tailored to the special characteristics of the target population remain valid.

I describe a clinic experience organized generally on the decentralized, comprehensive care model and aimed at a largely non-English-speaking population in the Chinatown area of San Francisco. San Francisco, already known for its multiracial character, has experienced an increase in its Chinese-American population from 65,000 in 1978 to more than 85,000 in 1982. The San Francisco General Hospital Medical Center (SFGH), the public institution serving the city's largely low-income and multiethnic indigent population, is situated at a considerable distance from the city's Chinatown, with indirect and difficult connections via the city's municipal transit system. A conveniently located private Chinese hospital has operated for many years in the heart of Chinatown, but its rates are beyond the means of many recent immigrants, and its use via Medicaid is limited for the reasons noted above. Prior to establishment of the SFGH satellite clinic in Chinatown, newly arrived Chinese-speaking immigrants of low-income status who sought care at SFGH were not only few in number, but also less likely to avail themselves of the early registration and close prenatal surveillance that low-income non-English-speaking patients should have. To rectify this situation, the hospital established a satellite clinic in one of the city's health department district public health centers (Health Center 4) in 1977. Virtually all of its patients, apart from the recent admixture of Indochinese refugees, are Chinese-speaking (about 90% Cantonese, 10% Mandarin) and more than 80% are unable to communicate in English. The Health Center, already actively involved in selected preventive medicine activities for a number of years, had an experienced, largely indigenous and bilingual multidisciplinary staff with ongoing well-child and family planning clinics, and with nutrition, health education, special services and public health nursing components already in place. Prenatal and postpartum care was initiated at weekly clinics at the Health Center, with SFGH providing an attending staff obstetrician and gynecologist and the hospital's high-risk prenatal clinic, other specialty clinics, laboratory and inpatient facilities for backup purposes and complications.

In reconciling the desire for culturally compatible outpatient care within easy reach of patients' homes and the need for an ultimate in-hospital experience for intra- and postpartum care, some exposure to the hospital

environment is desirable. Accordingly, all prenatal visits but two are conducted at the Health Center. Following an intake interview and history taking by a bilingual public health nurse, patients are escorted in small groups to the hospital for registration and preliminary prenatal laboratory tests. This presents an opportunity for a thoughtful guided orientation in which the strange and often frightening scenes of a modern metropolitan hospital are carefully interpreted and access to the necessary paperwork and laboratory tests is made as easy and as understandable as possible. A second, more leisurely and educational visit is made in midpregnancy, when groups of patients with their families are given a guided tour of the hospital along with instruction in where to go and the admission procedure for labor and delivery.

To maintain this degree of sensitivity to the anxieties of transitional immigrants, certain compromises with customary obstetric care are necessary. Screening for risk factors is done according to accepted standards of prenatal care. In the presence of overt intercurrent disease or significant risk factors, patients must of necessity be referred to the hospital high-risk obstetric clinic where the appropriate consultative and technologic resources are at hand. In many instances, subsequent surveillance and treatment regimens can still be achieved at the satellite clinic. The attention of a linguistically compatible staff in tune with a patient's culturally conditioned attitudes and beliefs about sickness and health is seen to compensate for the technologic limitations of the free-standing clinic.

It is unrealistic to assume that such bilingual, culturally sensitive care can be provided to most immigrants in the "melting pot" of America, with its multiplicity of linguistic or national origins. However, where geographic concentrations in neighborhoods of homogeneous ethnicity occur, and a critical mass of population to justify a local health care resource exists, the advantages of satellite clinics are many. This is particularly true among the Asian-American population, for whom the mastery of English is especially difficult.[4] The Chinese language has a basic structure that differs from that of English, has a tonal pronunciation and lacks a phonetic alphabet. Accordingly, few Chinese-speaking immigrants have even a partial or rudimentary familiarity with English. Linguistic subgroups and variable literacy, even in the native language, compound the problem, but are effectively dealt with by a bilingual staff that is familiar with the cultural nuances and economic class differences of the country of origin and less vulnerable to simplistic generalizations about persons of common ethnicity. None of these subtle features of clinic care appear in annual reports or clinic statistics, but they are nonetheless evident in the day-by-day interaction with patients. They call for a special tolerance of beliefs and attitudes toward health and disease that differ from the scientific system to which these patients are now expected to conform, and they affect compliance accordingly. A few examples from the Chinatown satellite clinic may suffice.

Obstetric screening procedures are often difficult for asymptomatic Chinese immigrants to comprehend. Many of them have had prior experience in rural settings or in Asian communities where Western technology does not exist, and where pregnancy outcomes were nevertheless generally satisfactory. In this context, amniocentesis, glucose tolerance tests, ultrasonography and non-stress testing are often perceived as meddlesome, dangerous, unnecessary and frightening. Compliance with these measures is, not surprisingly, less than complete. Accordingly, a special effort is made to explain procedures in readily understandable terms. More importantly, the clinic staff has learned to request such procedures with greater discretion, with a tendency to forego them when the indications are borderline and to insist on them only when serious consequences of noncompliance are anticipated.

Certain traditional health practices are tolerated or accepted with modifications, especially in the realm of nutrition and drugs. Chinese-American immigrants are admonished, as are their American counterparts, to avoid over-the-counter drugs during pregnancy. However, it is well known that many of them use herbal remedies either as "tonics" or for nuisance symptoms of pregnancy such as nasal congestion or constipation. To the extent that these are naturally occurring substances they are generally regarded as harmless, yet their widespread use and poorly understood ingredients suggest that more scientific investigation is needed to assume their safety when used during pregnancy. High sugar intakes are common, and in late pregnancy eggs scrambled with rock sugar are commonly used "to clean the system and lubricate the passage." Following delivery, restoration of the body's heat-cold balance assumes importance, and the hospital's labor and delivery staff are aware that drinking water offered to a just-delivered mother must be hot. In early puerperium, pig's feet in vinegar and later *gai jow* ("chicken whiskey") are consumed to contribute to the restoration of balance. Whether the latter contributes also to a predisposition to a late postpartum hemorrhage, as alleged by some Western obstetricians, remains conjectural.

A troubling phenomenon among recent Chinese immigrants is a predominant antipathy to breast-feeding. A study recently conducted in the Health Center 4 clinic showed that only 18% intended to start their babies on full breast-feeding, with 8% intending partial breast-feeding, 60% committed to bottle-feed and 13% undecided. It is recognized that most of these patients are working women (chiefly seamstresses) but only 15% of those who chose bottle-feeding listed the need to return to work as the reason. Moreover, nutritional counseling regarding the advantages to a child of even short-term breast-feeding in the six weeks before the mother's customary return to work is generally unheeded. While a variety of factors may be responsible for this phenomenon, the clinic's consensus regarding the resistance to breast-feeding despite health education and nutritional counseling is that it reflects a cultural

identification of breast-feeding with a primitive or agrarian past and a perceived adaptation to modern, urbanized and Western life-style. A special effort is currently under way to publicize among the clinic patients the resurgence of breast-feeding among American women and to provide additional educational reinforcement for breast-feeding during the critical early puerperal period.

Culture-specific family planning preferences appear in the postpartum clinic experience. Many of the patients observe a long period of postpartum abstinence that corresponds to the "doing the month" custom described by Pillsbury.[5] Hence, starting these patients on contraceptive regimens can be safely delayed. Among contraceptive alternatives, the combination of foam and condom is the most frequently preferred, and a high level of use and effectiveness results from both the additive effect of using dual methods and the self-discipline characteristic of this population. While interest in puerperal sterilization is often expressed, the degree of assimilation to a patient's new environment is heavily considered in sterilization counseling in order to avoid decisions that may later be regretted. A carry-over of traditional Chinese preference for male children is often expressed with a request for puerperal sterilization conditional on the sex of the newborn.[6]

For the record, a recent analysis of nonrefugee Chinese immigrant patients treated at Health Center 4 in 1982 showed a mean maternal weight gain of 13 kg (29 lb) and a mean infant birth weight of 3,276 grams (7 lb). Whereas it is believed that the combination of managerial and attitudinal approaches to this clinic population contributes to better pregnancy outcomes, this claim remains subjective and cannot be based on pregnancy outcome statistics. In the first place, the clinic population is admittedly selected for low or, at most, borderline risk status, with the remainder referred to the hospital clinics for more intensive care. Second, the Chinese-American population in San Francisco (including those recently immigrated) has long had a known record of low infant mortality and a low incidence of low birth weights. The reasons for this are largely rooted in traditional Chinese values and beliefs that are reflected in personal hygiene, nutritional habits and health behaviors, for which the clinic cannot take credit and from which much can be learned. By and large, such problems as out-of-wedlock adolescent pregnancy and smoking, alcohol and other substance abuse in pregnancy, which contribute so heavily to poor pregnancy outcomes, are rarely encountered in Chinese-American immigrants.

Thus, the success of this exemplary clinic experience is not measurable in organic terms. Nor can it be measured in utilization statistics because many of its patients are very recent immigrants who had some prenatal care before immigrating. Its achievement, in the minds of the clinic staff, lies not simply in the safe medical management of pregnancy, but rather in the use of prenatal care as a vehicle to assist recent non-English-speaking immigrants in their assimilation into American society. It consists of a conscious effort to seize each transaction implicit in prenatal care as an opportunity to promote self-reliance in the new immigrant. Thus, nutrition counseling not only assists in adaptation to new and unfamiliar Western foods, but uses this transaction to encourage familiarity with new English words pertaining to nutrition and food shopping. Health education and social services transcend immediate health concerns and assist in a variety of problem-solving situations in which the health center is seen as responsive to the felt needs of the community it serves. Moreover, the homogeneity and shared community interests of its clientele help to make the clinic a meeting place and attendance there a social event, a phenomenon that is readily apparent in the camaraderie and lively conversation occurring in the waiting room. Childbirth classes (and corresponding educational materials) are given in Chinese, and family participation in the obstetric experience is encouraged. A plan for an expanded project using essential prenatal education as a medium for the teaching of English as a second language has been proposed but has not yet materialized.

The acceptability of the Health Center 4 satellite clinic is reflected in its record of growth since its inception in 1977. From 55 mothers attended in 1977 with an average of about ten visits per mother, it grew to serve 245 in 1982, and once-a-week clinic sessions in 1977 have been progressively expanded to four sessions a week as the clientele continues to grow.

The lessons learned over the past five years in adapting community-based prenatal care to the Chinese immigrant population have recently been further applied to the care of Indochinese refugees. Many of the large influx of refugees arriving in San Francisco since 1978 have established residence within the catchment area of the Health Center 4 clinic. While they share many of the same problems of assimilation with Chinese-speaking immigrants from Hong Kong, Taiwan and the People's Republic of China, they exhibit much more cultural and linguistic diversity and have additional health problems related to poor conditions in their countries of origin. The experience of the Health Center 4 clinic in cross-cultural communication makes it a natural resource for care of this group with unique needs. It has required the establishment of separate clinic sessions where such interpreters of Vietnamese and Laotian dialects as are available can be used. (Khmer-speaking refugees have an alternative clinic resource.) The remainder of the support network arising out of the clinic's experience with Chinese-speaking immigrants and the relationship with San Francisco General Hospital Medical Center for inpatient care provides the comprehensiveness described earlier in this paper.

As noted, the focus of this clinic on a low-risk group precludes any objective measure of its impact on the health status of its clients. For the same reasons, cost-benefit analysis is likewise difficult. Clearly, comprehensive prenatal care, to the extent that it requires more time and the application of multidisciplinary skills, is

costlier than "standard" obstetric care. In this case, however, cost is kept to a minimum by integration of the clinic into a maternal and child health package of services including perinatal, well-child and family planning clinics that draw equally on the nutrition, health education, social service and outreach resources of the health center. The less readily measurable but equally important contribution that this approach to the health care of immigrants makes toward their self-sufficiency and sophistication as consumers of American health services must also be weighed in the cost-benefit balance.

The example of this clinic shows that if the constraints to participation by non-English-speaking immigrants are to be overcome, greater attention needs to be given in the organization of services to the cultural determinants of health behavior. In the effort to assist new immigrants into the mainstream of American life, medicine would do well to join forces with the growing field of medical anthropology.

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Cultural Aspects of Health and Illness Behavior in Hospitals

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Health care attitudes reflect the basic world view and values of a culture, such as how we relate to nature, other people, time, being, society versus community, children versus elders and independence versus dependence. Illness behavior determines who is vulnerable to illness and who agrees to become a patient—since only about one third of the ill will see a physician. Cultural values determine how one will behave as a patient and what it means to be ill and especially to be a hospital patient. They affect decisions about a patient's treatment and who makes the decisions. Cultural differences create problems in communication, rapport, physical examination and treatment compliance and follow through. The special meaning of medicines and diet requires particular attention. The perception of physical pain and psychologic distress varies from culture to culture and affects the attitudes and effectiveness of care-givers as much as of patients. Religious beliefs and attitudes about death, which have many cultural variations, are especially relevant to hospital-based treatment. Linguistic and cultural interpreters can be essential; they are more available than realized, though there are pitfalls in their use. Finally, one must recognize that individual characteristics may outweigh the ethnic and that a good caring relationship can compensate for many cultural missteps.

The special attitudes toward illness and treatment reflected in the behavior of members of various ethnic groups tend to be viewed by medical professionals as quaint or peculiar at best or an obstacle to good, efficient, modern medical care at the least. Because cooperation and compliance of a patient and a patient's family are vital to successful treatment, we cannot escape the need to overcome cultural barriers. For that we must increase our awareness of the diverse cultural attitudes about health issues in the ethnic groups we treat and to improve our skills in coping with these characteristics and adapting our treatment approaches to them. We must become aware of our own beliefs, values and attitudes as they affect our care-giving behavior.

Clearly, the cultural approach must be tempered with certain cautions:

- Cultural generalizations, if used in a hostile, condescending way, may not differ significantly from old-fashioned prejudice.
- Certain people, usually the postimmigration generation, *do not like* or are very uncomfortable about being given an ethnic label; they just want "to be treated like everybody else."
- Culture is not restricted to people of color.
- Intragroup individual differences may exceed intergroup differences.
- Our attitudes and blindness to our own tacit assumptions and biases may be more important than those of patients.
- Ultimately, a good caring relationship can overcome any cultural misstep.

Some definitions are in order. *Culture* refers to the sum total of acquired values, beliefs, practices, laws, customs, traditions, artifacts and knowledge possessed and expressed by a designated group, or "all human

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nongenetic, or metabiological, phenomena."[1] *Ethnicity* is that part of our identity derived from membership, usually through birth, in a racial, religious, national or linguistic group or subgroup with its associated culture.

Ethnic diversity contributes to the richness and creativity of society, though too great diversity can also lead to conflict. The healthiest, most dynamic and prosperous societies throughout history have tended to have the greatest ethnic diversity. Each group brings to the larger society the traditional ways of health care —prevention and treatment—acquired over decades or centuries, based on experience and accumulated knowledge. But health care means more than dealing with illness and pain; it reflects the basic world view and values of the culture that in turn influence health and illness behavior.

Cultural Values

Some essential *value orientations* that differentiate cultures[2] and ethnic groups are as follows:

- *The relationship to nature, which may be subjugating, submitting or in harmony with.* The predominant attitude toward nature affects the behavior of a person faced with illness—either actively intervening or passively fatalistic, or sometimes a combination of the two.

- *The view of people as basically good or true.* This outlook will affect one's view of causality, responsibility and hence action to be taken or not taken. Moralistic attitudes toward certain diseases such as alcoholism, acquired immune deficiency syndrome (AIDS), venereal disease, epilepsy and the like reflect such an outlook—that is, that disease is punishment.

- *The preferred or dominant way of interpersonal relating may be vertical, as in authoritarian cultures; horizontal, as in communal cultures; egalitarian and sharing, or individualistic.* Clearly, the preferred style affects decision-making processes between medical professionals and patients, between patient and family and between professionals and family—that is, who makes decisions and how critical issues in health care are decided.

- *Time orientation, whether toward the past, the present or the future, determines action taken or not taken about health matters.* Future-oriented persons will choose prevention (inoculations, prenatal care and so forth), whereas present-oriented persons will not. Present-oriented patients if they are asymptomatic may not take medicine and past-oriented patients may reject new or unfamiliar treatments.

- *A basic orientation with broad health care implications is that of being, doing and being-in-becoming.* A "doing" person will take action, a "being" person may not and a "being-in-becoming" person may do well with prevention, physical fitness, diet and the like, but may not be as activistic as the "doing" person with regard to symptoms.

- *Child versus elder-oriented values affect family priorities, attentiveness, protectiveness about children and elderly and who in the family makes decisions.*

- *Independence versus dependence orientation also contributes to health care behavior.* Independence in our society has often been equated with growth and maturity and psychologic health. Independence is not a developmental stage but a value. In Japanese culture, the ability to depend on others—to lean on others and be leaned on—is considered healthy.[3] The degree to which patients participate in their own treatment—taking or not taking responsibility for decision making or physical care—is determined in part by a patient's dependence or independence. There are obvious sex differences, men more often needing to be taken care of than women. Elderly men are more compliant because they expect to be taken care of. Very independent patients, who may deny their illnesses, can be hazards to themselves. But very dependent and helpless patients can be extremely draining and evoke rejection. This may explain why some alcoholic patients get rejected so often.

- *A global value orientation that has its effect on health care is that of* gemeinschaft *versus* gesellschaft.[4] Gemeinschaft refers to the concept and experience of "community," sometimes romanticized as the village of the "good old days" in which people are primarily involved with people—family and neighbors—and everyone works for survival, but work is otherwise secondary to personal interactions and social pleasures. Gesellschaft refers to "society" in the modern urban sense wherein people are primarily interested in accomplishments and products, whether material, economic, intellectual or creative, and in which personal relations are secondary. For example, a person of rural/peasant background walks off the job on short notice, if any, to go fishing with a cousin. This behavior is unfathomable to those of us from the gesellschaft world, but is not peculiar and may be commendable to those from the gemeinschaft world. In health care, for example, this same patient would view the relationship with a physician as being more important than the treatment. Such a patient might continue with inadequate treatment and not seek another opinion because of a congenial relationship with her or his physician. A gesellschaft patient sees the physician as a technician. Another example is a gemeinschaft patient's decision to neglect symptoms or treatment because of certain ceremonial or festive family obligations or activities, such as a wedding or baptism, or because of culturally designated responsibilities such as to continue being the breadwinner, hence not being able to take time off, and so forth. A gesellschaft person, being more self-oriented than a family/other-oriented gemeinschaft person, may act more quickly and therefore be a "better" patient by our medical standards.

Illness Behavior

Illness behavior refers to the nonbiological—that is, the psychosocial processes that are a product of social

cultural conditioning (values, world view and the like), part of a coping repertoire and a reflection of the meaning and usefulness of the "sick role."[5] Illness is not disease. Persons can have a disease and not feel it or not know or believe they are ill. *Illness behavior determines who is vulnerable to illness.* We will give four examples of illness behavior.

1. *Personality types.* Although psychoanalytic attempts to link personality with vulnerability to physical disease (such as peptic ulcers, neurodermatitis, asthma, irritable bowel syndrome) have been only minimally successful, the type A personality with its association with cardiac disease has been a useful model, and the type C (cancer-prone) personality may prove to be another one. These personality types reflect a behavioral configuration that involves other people, especially family. A person with the type A personality may be someone pulled by the extremes of the gesellschaft-gemeinschaft polarity.

2. *Death dips.* In statistical studies, initially of *Who's Who* biographies, Phillips[6] has shown that prominent people tend to die shortly after their birthdays, rather than before their birthdays, hence the "death dip." The phenomenon also occurs in association with important holidays and is clearly a cultural matter.

3. *Voodoo death.* Ever since Cannon's[7] first article, the phenomenon of death without physical cause following exile or similar rejection in tribal or peasant (gemeinschaft) cultures has fascinated the medical profession. The mechanism may prove to be an adrenocortical overload or autoimmune breakdown phenomenon, but culture (and expectation) is the predisposing factor. For some persons, admission to hospital itself might trigger a poorer outcome than home treatment for similar reasons—that is, the belief that hospitals are for dying.

4. *Social isolation.* Lynch[8] in his *The Broken Heart —The Medical Consequences of Loneliness* and Gunderson and Rahe[9] in their epidemiologic work on life change stress have presented convincing arguments about the connection between ruptured personal relationships—marriage being the foremost—and the subsequent appearance of major disease, especially heart disease. Separated people are the most vulnerable, even more so than the divorced and bereaved.[10]

Illness behavior determines who will agree to become a patient. About two thirds of people who have an illness do not see a physician, hence choosing not to become patients. Although the cultural determinants of patienthood are more evident with psychiatric disorders—some cultural groups will not consider seeing a doctor or any healer for symptoms of depression or alcoholism—even physical symptoms are not exempt from this behavior. Rather than by our medical criteria, persons may choose to be patients on the basis of severity of pain (which also varies with culture), offensive appearance or impairment of certain functions, such as ability to work, bear children, have sexual intercourse or sleep. Some persons may choose to be patients for purposes of rejuvenation, cosmetics, weight loss, ridding oneself (or family and community) of bad spirits or for economic gain (that is, litigation, compensation, maintaining disability status or obtaining sick leave).

Illness behavior determines how one behaves as a patient. As implied above, a patient's behavior will reveal significant culturally determined characteristics. Compliance and cooperation, resistance and rebellion, pessimism and despair, besides reflecting individual personality, will reflect cultural attitudes. What does it mean to be ill? A culture that teaches that illness is a punishment for sin or a curse will produce a different reaction than a culture that emphasizes that to be ill is to be weak, unmasculine or irresponsible. If illness means economic loss or gain, behavior will correspond in obvious ways. These cultural meanings just as importantly will affect a family's behavior, whether the family is supportive, nurturing, attentive or rejecting and avoiding of a patient. In most instances, a rural or peasant (gemeinschaft) family will be more attentive, if not intrusive, than a typical urban cosmopolitan family who leaves the care up to medical professionals. A gemeinschaft family has culturally designated roles and behavior vis-à-vis ill or disabled family members that have been formed over generations. For example, women may have nurturing and nursing roles, but not men. In some languages, for instance, Japanese, there is no name for a male nurse. The primary decision maker and primary caretaker are roles that have been predetermined in many cases, and they usually do not correspond to a cosmopolitan medical system's assignment of roles.

The hospital setting illustrates the culture-based illness behavior most clearly because of the greater seriousness of the situation, the particular structure of hospital organization and roles, needs and responsibilities. First, *culture influences who makes decisions about a patient's treatment.* From the professional viewpoint, by custom and common law, the physician, with a patient's consent, makes the decisions. From a patient's and patient's family's viewpoint, the picture can be very different, depending on the culture. For instance, there are authority figures inside and outside the family. Reaction to these authority figures may depend on the culture's general attitude toward authorities—that is, whether or not it is a vertical system—and depending on the hierarchy of the authority figures. A nontrivial example would be who takes priority, grandmother or American physician, in terms of decision making. For some ethnic groups the primary decision maker may not even be a relative, as is the case, for example, with Gypsy patients.

Authority and responsibility have a complementary relationship, that is, if patients look to another authority for decision making, they will not feel responsible for their own care, nor be expected to be responsible for this care. Because the decision maker may be taken for granted by a patient or patient's family, and because the medical staff may act like they are the de-

cision makers, patients may not reveal who really makes decisions for them in medical matters, so as not to offend the medical staff. Even staff familiar with a particular culture may not help unless asked to do so. When you do not get a clear-cut response about a treatment decision from an Hispanic or Asian patient, he or she may be waiting to first have a consultation with a respected family member. And that person of authority may be the only one who can give a medical history. This also relates to the general matter of which and how many family members may visit a patient. Physicians should remember that the group has a healing function.

Communication in Hospital Settings

The hospital situation highlights special problems of communication with patients of ethnic groups because the hospital experience is so intrusive and so many different professionals and paraprofessionals have access to patients. This is added to the sense of strangeness and high anxiety connected with being in hospital. Why do Soviet immigrants fear being removed or getting out of a hospital bed when other patients are difficult to keep in bed? Etiquette, modesty, touching and spatial distance convey significant nonverbal messages about relationships and traditions that, if violated, can undermine rapport and even disrupt treatment. Most non-American cultures pay great attention to respect and etiquette, probably because of the vertical interpersonal nature of many societies, and the need to establish rules for every interaction. Certain cultures even use different dialects or grammatical forms when communicating up or down the class or caste system. Anglo-Americans tend to be informal and appear rushed if not brusque. This is interpreted as uncivilized, rude and disrespectful. In many parts of the world, one must first sit, chat and have tea or coffee before getting down to business, at least briefly when there is urgency. Paying respect to a family elder may be expected. For example, in the treatment of black children, lack of compliance may be traced to a failure to consult the child's grandmother. Hospitals could serve tea or, if not, hospital personnel could exchange pleasantries with patients and families before plunging into technical examination or care. We should beware of mispronouncing names, especially of patients with tonal languages like the Chinese, Thai or Vietnamese. For example, *ma* can mean mother or horse in Mandarin, depending on the inflection. Mispronunciation does not engender natural trust and respect, and humiliation cannot enhance recovery.

Misuse of terms of address is the most common and the first offense to sensibilities. The inappropriate use of first names before a relationship has been established —except for children—or the use of pseudo-kin terms, such as "auntie," "uncle," "grandma," "pop" and the like, may offend or create discomfort. A rule of thumb is, after exchanging introductions, "Mrs Smith, I am Dr Jones," one should ask "How would you like me to address you?" or "How do you like to be called?" Addressing women patients as "dear" or "honey" is an unpleasant vestige of condescension toward women and an unwarranted intimacy.

Touching a person's body has special meaning and one must know the rules, or at least ask, so as not to upset patient and family and have them lose respect for the examiner and hospital. The most obvious problems involve examination of private parts by the opposite sex, especially among Muslims, some Roman Catholics and Orthodox Jews. But less obvious are concerns in some cultures about the sacredness of the head, which should not be touched casually. If in doubt, ask. Gypsies have especially strong feelings about the separateness of the upper (sacred) and lower (profane) areas of the body. One cannot first take a pedal or femoral pulse and then touch the chest, head or arms. They are very concerned about pollution, and even go so far as not to wear hospital-laundered garments that have been worn by non-Gypsies.

Proxemics is the study of the nonverbal communication expressed by the distance between people.[11] Persons of different cultures tolerate and feel comfortable at different distances, a circumstance that can lead to numerous misunderstandings. For example, Arabs tend to stand and speak very close to each other, within "breathing distance," whereas Americans require a few feet and the British perhaps several more feet between. One can imagine the ballet of an Arab trying to talk with an Englishman who keeps stepping back, the former feeling puzzled and rejected, the latter feeling pressed and pushed upon. The arrangement of furniture may communicate similar cultural traits through the distances between chairs, their mobility, the desk as barrier and the open or closed door.

Verbal Communication Problems

Three verbal communication problems deserve attention. The first is the use of interpreters, whether family members, volunteers or designated employees. Clearly, the use of interpreters compounds the difficulty inherent in cross-cultural communication. Interpreters may distort information because of their own values. For example, a Chinese interpreter would not convey a physician's directive to the Chinese husband of a patient to stop beating his wife because such is the traditional prerogative of a husband in that culture; an interpreter may distort because he or she has a wish to impress the physician, or not to embarrass the physician (or nurse), or to make a situation appear less serious, or because the interpreter does not consider some of the information significant, and so forth. If a patient is expressing delusions or describing hallucinations, an interpreter may, with slight alteration, make these symptoms sound rational, so as to make sense out of them. In cross-cultural work one must match eccentric thoughts and behavior against the prevailing standards and beliefs of that culture. For instance, seeing spirits and ghosts may not equate with visual hallucinations per se in a culture in which such experiences are common.

A second problem may involve English as a second

language, whether the patient's or the physician's. Even non-American English speakers may be misunderstood. For example, after a hearty meal, an American might say "I feel stuffed," which to a Briton colloquially means to have had sexual intercourse! But the linguistic issues go beyond misunderstanding words, which occurs even between generations (such as "Valley girls' " or musicians' hip patois). These involve the distorting effects of unusual inflections and syntax. The resultant problems often are more emotional than cognitive. Filipinos may sound evasive and insincere; South Asians or Indians may sound "pushy." The consequences, even in the medical realm, have been very serious accusations and poorly understood (or not believed) defenses against medical negligence. Anthropology Professor John Gumperz of the University of California at Berkeley has studied and testified in such situations. There is also an excellent film, "Crosstalk,"[12] that illustrates some of these problems.

A third verbal problem is the magical meaning of words. Even sophisticated people sometimes act as though naming a disease will cause it. Hence, there may be a reluctance to raise questions about cancer, alcoholism, suicide or other taboo diagnoses or possibilities—such as skin diseases or Hansen's disease in some (tropical) cultures. Some Hispanic and rural persons may not dare tell their physician what is really bothering them for fear of the magical effect of naming. We also need to be cautious about being blunt in order not to precipitate panic.

An extreme communication problem is when there is none at all, such as the case of a Cambodian boy with an acute appendicitis who was rushed to emergency and to the operating room of a California hospital without the benefit of explanation in the absence of an interpreter. The medical staff was oblivious to the fact that the boy was expecting to be executed by evisceration, a common form of execution by the Khmer Rouge in his recent past. That he did not die from voodoo death was a miracle in itself.

Diet and Medication

Cultural practices may impede or even negate cosmopolitan medical care. This is especially true with compliance with diet and medication. Dietary practices are probably the most unshakable learned behavior, and food has great symbolic importance. But culturally relevant and acceptable diet is easy to arrange and often cost effective. Unacceptable foreign food is very demoralizing and could logically inspire a patient to question the relevance of the medical treatment itself and the competence of medical staff. Contributing to attitudes toward diet and medicines is the hot-cold concept derived from Hippocratic humoral medicine and spread throughout the world by Arabic influence and later, in turn, Spanish colonialism.[13-15] Although the current forms of this system vary by geographic region and national boundary and basically have no physiologic or nutritional basis for the determination of which substance (or disease) is labeled hot or cold (including drugs as well as foods), the concept of balance involved can be used constructively. We can adapt, for the sake of gaining compliance, our prescriptions and dietary orders to the hot-cold system by serving medicines either in or with acceptable foods or beverages. For example, some cultures consider penicillin a "hot" substance and therefore will refuse an injection in case of a fever, but orange juice is a cold food. Penicillin given in orange juice might be acceptable. A baby with dysentery (a cool disease in Guatemala) may be denied water because the water is considered a "cold" substance, and sick babies need to be kept warm. In other words, prescribing and walking away is not enough. It is necessary to determine whether or not a prescription will be implemented. The concept of balance and neutralization, however, can be used to explain our treatments and obtain cooperation from a patient and family.

Other possible blocks to compliance can be postpartum and menstrual taboos whereby a culture prescribes what may or may not be taken into the body or put on the body at those times. A postpartum woman in some areas of the world needs to be kept hot (even in the tropics) and therefore cannot eat fish (the most available source of protein and considered "cold"). One of us (J.H.) had an Hispanic patient with depression who after several months of lack of response to antidepressants indicated that she did not take the medication for about ten days during and after her menses. Another problem with compliance occurs with medication given prophylactically or on a long-term basis when no symptoms are evident, such as for tuberculosis or epilepsy. These situations are just extensions of the problems also seen with educated and sophisticated patients.

Cultural Differences and Pain

Regardless of illness and health beliefs, the central symptoms for which all people seek help is pain. But, the perception and experience of physical pain and psychologic distress vary among cultures and the physical and psychologic distress varies independently. Our perception of pain or distress colors our inferences and empathy or sympathy toward the experience in others. Not only does the experience of pain and distress vary, but the readiness to complain varies culturally. Furthermore, we have prejudices about how others experience and react to pain that alter our sensitivities. In some cultures complaints are rewarded with attention, affection and comforting behavior, which probably reinforces that style of reaction. American Jewish and Italian parents have been noted to be especially indulgent and attentive to their children regarding pain, perhaps thereby encouraging sensitivity to pain.[16] Other cultures reward stoicism or punish complaining children, resulting in adults who may actually feel less pain. But the interaction between the learning and genetics of pain sensitivity has still to be delineated. An excellent study of the cultural issue was done by Davitz and Davitz in their *Inferences of Patients' Pain*

and Psychological Distress—Studies of Nursing Behaviors,[17] in which the attitudes of 4,000 nurses from 13 countries were compared. We will summarize some of the findings by presenting the polarities:

- Nurses generally see patients of lower socioeconomic status as suffering more (except for cardiac patients) than patients of higher socioeconomic status; women suffer more than men, but women of high socioeconomic status suffer the least. (Note the role of identification with persons of one's own socioeconomic status.)
- Nurses tend to infer a greater degree of psychologic distress than of physical pain in evaluating patient suffering.
- Nurses see Jewish and Hispanic patients as suffering most, Asian and Anglo-Saxon/Germanic patients as suffering the least and other ethnic groups falling between.
- Black nurses tend to infer a greater degree of psychologic distress than white nurses, regardless of patients' race.
- Nurses of northern European background inferred the least painful suffering in patients. Nurses of African and south and east European backgrounds inferred relatively high patient suffering (each group may be projecting its own experience of pain).
- Nurses from Asian countries showed a great range of national differences in inferring psychologic distress and physical pain, Koreans inferring the most of both and Japanese next, whereas Taiwanese and Nepalese inferred the least psychologic distress, and Thais were intermediate; Thai nurses inferred the least physical pain, with Taiwanese, Nepalese and Japanese inferring more physical pain, increasing in that order. The diversity certainly shows how difficult it is to generalize on the basis of race.
- Puerto Rican nurses inferred psychologic distress to be very high and physical pain to be very low. (They explained this in terms of discounting some of the pain complaints because of the "emotionality" of their countrymen.)
- Jewish Israeli nurses inferred relatively low psychologic distress and physical pain—differing markedly from non-Jewish American nurses' views of Jewish patients, again highlighting cultural over racial (genetic) factors.
- English, American and Belgian nurses expressed the lowest inference of physical pain. (I recall my clerkship at Guys Hospital in London when a distinguished professor made the point that if he were in pain he would prefer to suffer and think clearly so he could read his favorite books rather than take opiates.)

This last finding has wider implications because American nurses have contact with and serve people from many different backgrounds and different ways of expressing feelings, a reflection of the heterogeneous American population. There is every reason to believe that what is true for nurses is true for physicians. If a nurse (or physician) infers less pain or distress than a patient complains of, the patient is labeled a complainer, evoking anger, irritation and rejection by the nurse (or physician), or at least lack of support. This no doubt contributes to a patient's demoralization and possibly delayed recovery and a vicious cycle of more complaints and demands and more rebuffs. The opposite might occur if a nurse infers too much pain or distress. In that case a patient (and family) might develop excessive anxiety and apprehension. There is an optimal amount of anxiety,[18] and rejection and hopelessness are never helpful or health-inducing.

Religious Beliefs

Regarding hope, let us briefly discuss religion. Religious beliefs and practices are part of culture, yet our American society behaves ambivalently toward religion. We fluctuate between secular life-styles and values and periodic religious fervor and even fanatic bigotry. But there are people for whom religion is a daily presence, a high proportion of whom may be among the so-called ethnic minorities. For these people, being in hospital should not mean that their religion must be excluded. In fact, prayer to one's God gives comfort and hope and may be lifesaving. Religious articles and symbols, even amulets, are important and need to be treated with respect and sometimes encouraged. Even a secular physician or nurse has her or his amulets, such as titles, white uniforms, dangling stethoscopes and the like. Respect is an issue, even for those who do not want religion imposed on them. For Muslims (and Orthodox Jews), bovine, not porcine, insulin must be given, though rules for Jews can be suspended to save a life. It should be remembered that the largest Muslim populations are not in the Middle East but in Indonesia, Malaysia, Pakistan and Bangladesh. We may say, "Well, how would the patient know?" (that he or she received porcine insulin); the response might be, "If he knew it might kill him," because honesty, trust and ethics are major components of the healing relationship.

Last, as ever, comes death. Anglo-Saxons' and northern Europeans' reactions to death tend to be restrained, except perhaps for the Irish at a wake, whereas many other cultures encourage and even require great demonstrations of feelings. Similar differences exist regarding the handling of the deceased, the farewells, the preparations for burial and the question of autopsy. Anticipatory plans for death, even asking an appropriate religious figure to come to see a patient, may be considered by some Middle Eastern people extremely bad taste and an indication of not trying to save the life. It is advisable to deal with a family through an intermediary such as a distant relative, if possible, to determine what the family wants and expects.

Conclusion

Obviously the complexities of many cultures are such that one cannot master any but one's own. But an

approach can be developed. Like the psychotherapist, we can all ask, "What do you mean by that?" A genuine interest, a willingness to give a little extra and a respect for customs can go a long way toward improved communication and compliance, and thus a better outcome. We should ask about customs and practices, listen, explain and correct for our own cultural biases (for instance, regarding pain tolerance), use intermediaries and interpreters, colleagues and other hospital staff and be aware of the possible distortions in transmission. But, as stated above, a good caring relationship is still the greatest insurance against, and antidote for, the inevitable cultural mistakes.

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The Changing Alaskan Experience

Health Care Services and Cultural Identity

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Before Western contact, Alaskan Native populations were self-sufficient in their health practices. Slowly, the Native health care system was replaced by a Western one which was highly effective in treating infectious diseases. As infectious diseases were brought under control by the Indian Health Service, the emergent leading health problems were related to violence, attributed in part to cultural disintegration. New types of Native health providers and new Native-controlled institutions evolved to provide culturally appropriate health and mental health services and to promote a stronger cultural identity.

In contemporary American society, there is a tendency to regard health and health care services as a private matter between physician and patient. However, health care—including health practices, providers and institutions—has another level of meaning in society—that is, as a component of culture and cultural identity. This is perhaps more visible in a cross-cultural setting, as illustrated in the evolution of health services for Alaskan Native populations.

The transition from the Indian Health Service (IHS) Alaska Native Health Service (ANHS) to Native nonprofit corporations as the primary providers of health care services in rural Alaska may be regarded as burdensome to Western-trained health professionals. However, the change in health services is part of a larger cultural evolution in which health care has played an important role; it has promoted a cultural revitalization that may be the key to solving the most pressing Native health problems today.

Background

Alaska is culturally and ecologically diverse. Currently a minority, the 64,000 Alaskan Native peoples who live primarily in rural areas, are descendents of the original inhabitants of the region. Eskimos originally occupied the coastal tundra areas, Athabascan-speaking Indians inhabited the boreal forests in interior Alaska, Tlingit and Haida Indians predominated in the rain forests of the southeastern panhandle and Aleuts subsisted along the chain of Aleutian Islands that stretches for a thousand miles into the Pacific Ocean. Within each of these cultural groups, there were subgroups that had distinctive dialects and social organizations.

About 70% of the 400,000 people living in Alaska are in the three largest cities where health services are similar to those in other parts of the United States. The remainder are scattered in towns and villages ranging from 25 people to 10,000 in a geographic area about a fifth the size of the contiguous United States. Few of the 180 villages are connected by roads, most relying on boats and airplanes for their linkages with the rest of the state.

The Treaty of Cession, which transferred Alaska from Russian to US ownership in 1867, entitled Alaskan Native peoples to the same laws and regulations that the United States adopts with regard to other Native American peoples. As medical historian Robert Fortuine[1] explains, this entitlement did not result in comprehensive health services for Native Americans until nearly 90 years after the Treaty of Cession.

> Throughout the Russian period and into the American era, however, despite the fact that a primitive system for health services existed, it really did not touch the lives of most natives, who after all lived far from the settlements. In the interior and in most coastal villages, life went on as before. Whatever health services were available were provided in the old way by family members or native healers.[1(p8)]

Whereas each culture in Alaska differed in specific approaches to promoting health and treating sickness, there was widespread knowledge regarding proper nutrition, medicinal uses of local plants, midwifery, setting

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ABBREVIATIONS USED IN TEXT

ANHS=Alaska Native Health Service
OEO=Office of Economic Opportunity

broken bones and realignment of dislocated joints.[2-8] However, ethnomedical practices of Alaskan Natives were unable to stop the devastating epidemics of measles, influenza, smallpox, tuberculosis and venereal diseases that were impervious to treatment by traditional healers,[9] thereby discrediting Native healing practices. An Army Corps physician in Fort Egbert, Alaska, in 1906 located an Athabascan man "who sheepishly admitted that he had been a medicine-man, but had given it up because the missionaries and police opposed the practice."[10] Not only were traditional curing practices discouraged, Alaskan Natives were also pressured by missionaries, schools and government to discontinue other customs and to abandon their Native languages.

The Snyder Act of 1921 established the broad statutory authority for the federal government to provide health care services to Native Americans. Despite the growth in numbers of hospitals and Western-trained physicians and nurses in Alaska during the Territorial period, a comprehensive health care system was slow in developing:

> For the first half of this century, primary care in most villages was largely in the hands of the schoolteacher, the missionary, or perhaps, on occasion, the trader. The Bureau of Education and later the BIA [Bureau of Indian Affairs] made available a handbook, a few drugs, and basic medical supplies to each of its teachers, who got along as best they could. The local villages were visited from time to time by a traveling nurse or even more infrequently by a doctor from the Bureau of Education, the ANS [Alaska Native Service], a mission, or perhaps a Coast Guard ship.[1(p30)]

With impetus from the Parran Report[11] and transfer of health services from the Bureau of Indian Affairs to the US Public Health Service in 1955, this loosely organized complex of health services was developed into a highly effective system to combat the critical health problems of Alaskan Natives at that time. As an agency of the Indian Health Service in the Public Health Service, the Alaska Native Health Service established a decentralized program with seven service units covering the entire state. A joint ANHS and Territorial Government effort to combat tuberculosis in Alaska succeeded in reducing the incidence rate from 605 per 100,000 in 1950 to 100 per 100,000 in 1960 (Figure 1). Successful clinical trials of the newly developed isoniazid prophylaxis in Alaska further reduced the incidence of tuberculosis, thereby freeing hospital beds and changing the provision of health services from a predominantly inpatient emphasis to ambulatory chemotherapy.

Following the assault on tuberculosis, the ANHS resources and personnel were marshalled to reduce the extraordinarily high rate of infant mortality in Alaska (Figure 2). The Indian Health Service in Alaska targeted its efforts to improve maternal and child health services, provide greater access to primary care and

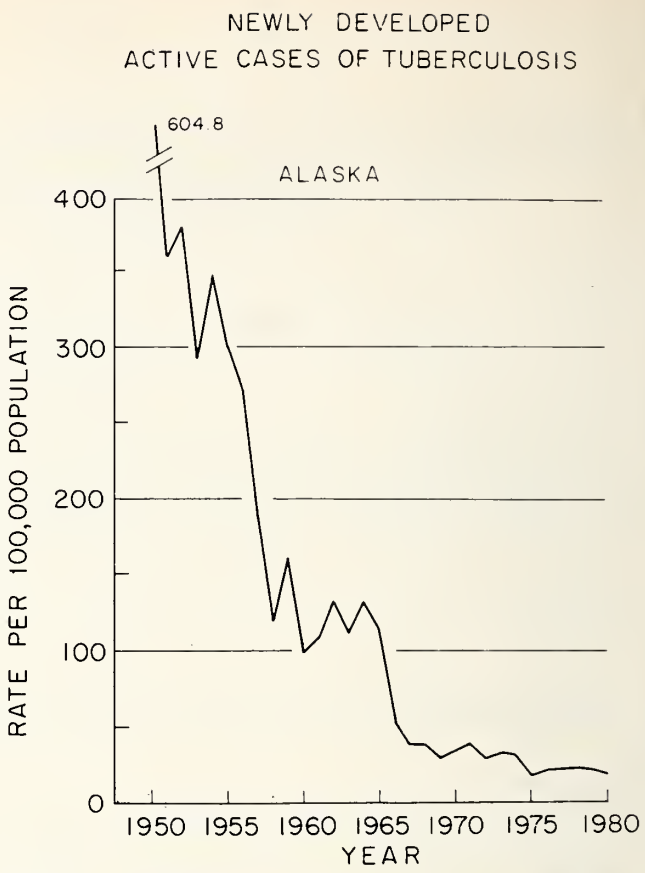

Figure 1.—Incidence of tuberculosis in Alaska, 1950-1980. From Alaska State Health Plan.[13]

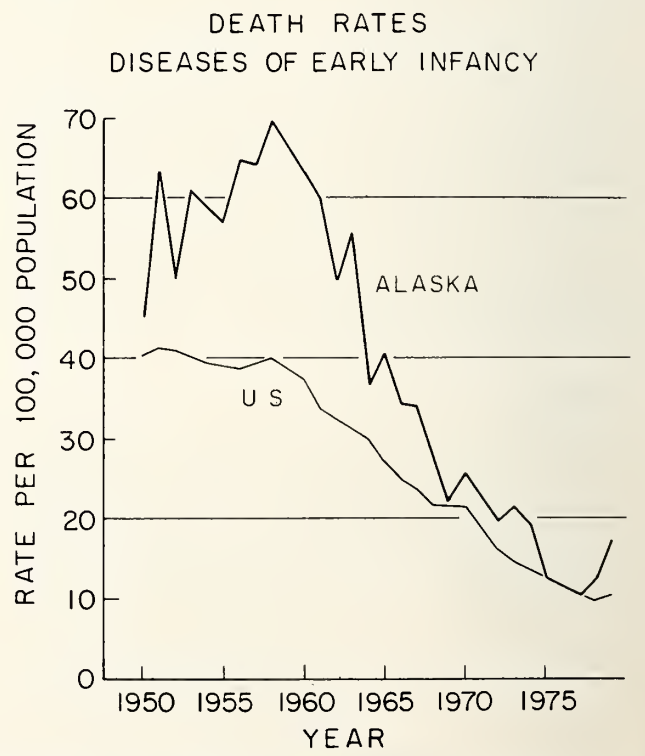

Figure 2.—Infant death rates in Alaska, 1950-1980. From Alaska State Health Plan.[13]

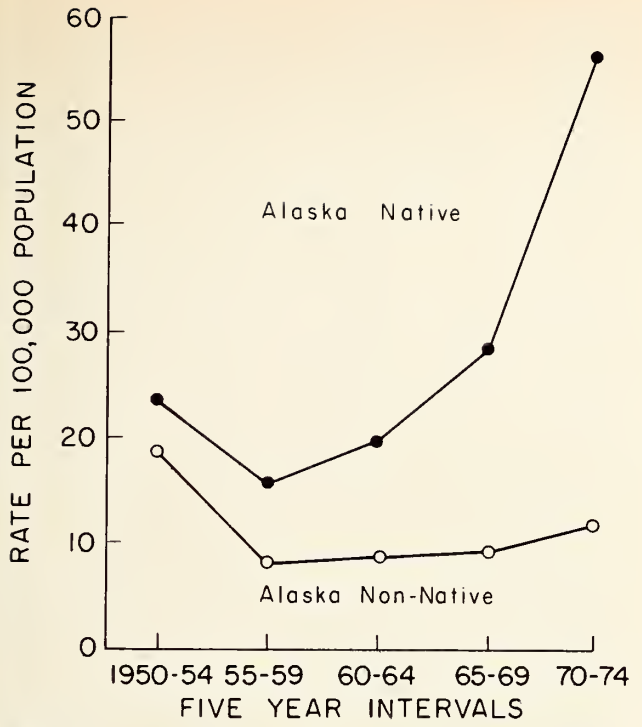

Figure 3.—Alcohol-related death rates in Alaska, 1950-1974. From Alaska State Health Plan.[13]

construct individual and community water and waste disposal systems in Native villages. The successful performance of Native volunteer chemotherapy aides in the villages during a tuberculosis campaign in the 1950s led to training of Native persons as village health and sanitation workers. A special appropriation from Congress in 1968 enabled ANHS to hire and train Community Health Aides to provide primary medical care in the villages.

As infant mortality declined, behaviorally based health problems emerged as the leading health problems in Alaska (Figure 3). At the present time, the leading cause of death in Alaska is a cluster of problems labeled "violence," which includes accidents, suicide, homicide and deaths due to alcohol.[12,13] A key feature in this high rate of death due to violence appears to be the use and abuse of alcohol and other drugs.[12] Alcohol and drug abuse, and the morbidity and mortality that result from them, have not been responsive to the types of interventions that ANHS so successfully developed to combat tuberculosis, reduce infant mortality, decrease the incidence of chronic otitis media and improve environmental health. Rather than technologic innovation, it appears that social and cultural innovations are required to solve the most pressing health problems in Alaska today.

Emergence of Native Nonprofit Corporations in Alaska

The "War on Poverty" legislation signed by President Lyndon Johnson in 1964 had a tremendous impact on rural Alaska.[14] From 1965 to 1968, the federal Office of Economic Opportunity (OEO) spent $20 million in Alaska on projects that provided leadership training for Native peoples, grassroots political organization, greater Native involvement in the administration and policy making of health, economic and social service programs and the foundation for the political battle to settle the Native land claims issue.[14] With OEO funding, the Yukon-Kuskokwim Health Corporation was formed in Alaska in 1969. This Eskimo-dominated health corporation, headquartered in Bethel and serving 78 villages in the Yukon-Kuskokwim delta, became a demonstration project. In 1970 this model was replicated in the Nome area with the formation of the Norton Sound Health Corporation, another consumer-controlled nonprofit corporation.

Alaska is now served by 12 regional, nonprofit locally controlled health authorities with non-overlapping service areas that encompass the entire geographic area of the state (Figure 4). Two pieces of legislation enabled the development of this unique health care system. The Alaska Native Claims Settlement Act of 1971 defined 12 culturally cohesive regions in Alaska[15] that have become the standard geographic units for the planning and provision of a variety of services. After passage of the Alaska Native Claims Settlement Act, the nonprofit corporations that had been formed in each region to lobby for the land claims redirected their goals towards improving health, social services and education in the regions. This process was assisted by a second significant piece of legislation, PL 93-638, The Indian Self-Determination and Education Assistance Act. This law, enacted in 1975, mandated that federal agencies contract with tribal organizations to provide services. As the functional equivalent of tribes, the regional nonprofit corporations in Alaska proceeded to contract with the Indian Health Service. Thus, PL 93-638 provided a source of funding for regional nonprofit health corporations in Alaska. Additional planning dollars were made available to the corporations by the Indian Health Care Improvement Act (PL 94-437), which required tribal-specific health plans for improving health status, ascertaining Native perceptions of problems and proposing culturally acceptable solutions.

With the exception of the North Slope region where health services are provided by a local governmental entity (the North Slope Borough), the Native health authorities in the regions are organized as nonprofit corporations, either specifically for the purposes of providing health services or more generally to provide health and social services. In addition to contracting with the Indian Health Service, many of the regional nonprofit corporations contract with the state of Alaska to provide community mental health services, emergency medical services, alcohol treatment services and public health nursing services. The nonprofit agencies also compete for a variety of grants that may be available from the state and federal governments and private foundations.

The scope of services varies from corporation to

corporation, depending on the decisions of the boards of directors who generally attempt to minimize their risks by opting for low-capital, labor-intensive programs.[16] Over time, however, the regional nonprofit corporations have accepted increasingly larger responsibilities for the provision of health services. Norton Sound Health Corporation owns and operates a regional, acute care general hospital in Nome. The Bristol Bay Area Native Association manages and operates the Indian Health Service Hospital in Dillingham. Today the nonprofit corporations offer some or all of the following services: hiring, training and supervising Community Health Aides; temporary housing for patients and their families who must leave their villages to be delivered of their babies or to avail themselves of other hospital-based services; environmental health services, including the training, supervision and quality control of village sanitation workers; eye care services; preventive dental services; alcohol and mental health treatment services; community health education; construction and renovation of village clinics; outpatient care in conjunction with an Indian Health Service hospital, and hiring and supervising outreach workers, called Community Health Representatives.

Culturally Appropriate Services

Most of the regional nonprofit corporations have boards of directors comprised of representatives from the villages in the region served. An underlying philosophy has been to develop and provide health care services in a culturally appropriate manner using trained health personnel drawn from persons in the region. Oftentimes, the mid-level managers and professional personnel in these nonprofit corporations are non-Native persons for whom it is necessary to define more clearly the cultural values of the people they serve. At the same time, Native people in the regions are defining their own cultural values as part of the revitalization of a cultural identity (Creed J: NANA region works to revitalize Inupiat spirit, *Tundra Times,* 1981 Jun; 18:1,16). In northwest Alaska, for example, a "Spirit Committee"—formed to identify traditional Inupiat values and to make recommendations about how those values can be maintained in both public institutions and family life—compiled the following list: "knowledge of language, sharing, respect for others, cooperation, respect for elders, love for children, hard work, knowledge of family tree, avoid[ance of] conflict, respect for nature, spirituality, humor, family roles, hunter success, domestic skills, humility, responsibility to tribe" (*Tundra Times,* 1981 Jun; 18:1,16).

In an effort to preserve traditional health care practices and integrate them with modern medicine to foster cultural pride and a sense of well-being, several of the regional nonprofit corporations have commissioned studies to record and evaluate the efficacy of traditional

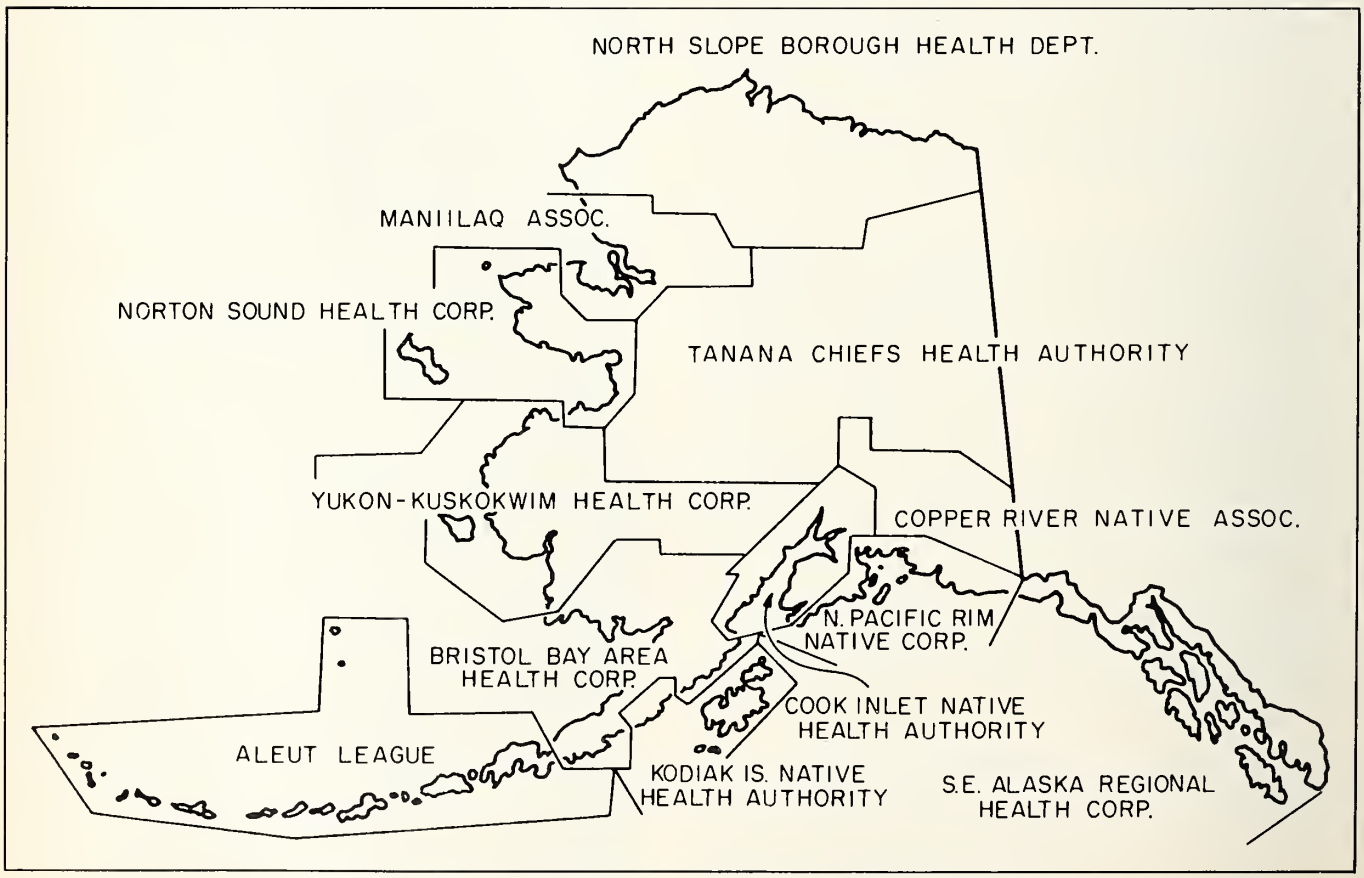

Figure 4.—Native regional nonprofit corporation boundaries in Alaska.

Native healing practices.[17-19] Native nonprofit corporations also have sponsored Elders' Conferences in which older Native persons share their knowledge on subjects central to the independence and survival of Native people. Health planners and administrators have used the Elders' Conferences as an important forum to elicit ideas for culturally appropriate program development.

A unique program evolving from the Inupiat Ilitqusiat (Spirit Committee) movement is the Eskimo Tribal Doctors program in northwest Alaska. Under the sponsorship of the Maniilaq Association, the Eskimo Tribal Doctors program integrates Eskimo medical practitioners who use traditional healing arts, such as massage and "poking,"[20] into the Western-dominated health care system. In addition to hiring Eskimo healers selected by their villages, the Eskimo Tribal Doctors program is recording the knowledge of these healers and arranging for younger persons to study with older practitioners. As Book and co-workers describe elsewhere in this issue, the Eskimo Tribal Doctors program also sponsors periodic retreats to Serpentine Hot Springs under the supervision of Native healers.

Rural community mental health centers in Alaska, many of which are under the organizational umbrella of regional nonprofit corporations and some of which serve vast geographic areas, have been especially concerned about developing culturally appropriate services. Experience has shown that many of the smaller Native communities "will neither use nor likely benefit from a case-oriented urban service model."[21] Failure of the urban model in rural Alaska has stimulated innovations that are more culturally appropriate for the villages. The Tanana Chiefs' Mental Health program, for example, has sponsored poster contests on alcohol and drug abuse in the schools, produced a comic book about fetal alcohol syndrome for teenagers and conducted a survival camp in which Native elders teach young persons how to survive in the old ways without modern amenities. The McGrath Anvik Community and Family Services program mandate includes "developing opportunities for concerned community members from throughout the region to meet and share ideas and strategies for positive change and growth."[22] In these programs, the content and direction of mental health services are developed by the Native people living in the regions; there is no rigid adherence to clinical styles characteristic of Western-trained professionals.

Community Health Aides

Community Health Aides are both the cornerstone and the symbol of the new health care system that has evolved in Alaska. Statewide health planning efforts over the past six years formally recognize that it is neither desirable nor economically feasible to have a physician in every community in Alaska.[13] At the same time, access to primary medical care is essential for Alaskans living in remote communities. Since 1968, this has been accomplished by Community Health Aides. Virtually every predominantly Native village in Alaska has at least one Community Health Aide. The larger villages have two or three health aides and at least one alternate. Health aides and alternates are selected by their village councils and hired by the regional nonprofit corporation, which is also responsible for their training and supervision.

A survey of Community Health Aides in Alaska in 1977 provided the following profile[23]: Typically, the aide is a 38-year-old Native woman with three children younger than the age of 21 years; she has lived in her community since birth; she has an eighth grade education and has been a health aide for 7.5 years. Many of the health aides served their communities without pay as chemotherapy aides, midwives or health liaisons before the inception of the Community Health Aide Program. In recent years, health aides have tended to be younger and better educated.

The current statewide standardized curriculum,[24] divided into three sessions of three to four weeks in duration, minimizes the amount of time that health aides are separated from their family and village. Continuing education and supervision are provided by itinerant Health Aide Trainers, who are usually mid-level practitioners, and by itinerant physicians. In recommending that the Alaskan Health Aide Program be replicated as a model for other sparsely populated areas, Haraldson[25] cites as one of the strengths of the program the training that does not create a "brain drain" characteristic of developing countries, which send indigenous persons to Western medical centers for extensive medical training and then tend to lose them to urban areas.

Health aides are provided with medical equipment, medicines, standing orders[26] and either a radio or telephone satellite communications equipment whereby they have daily contact with physicians at ANHS service unit hospitals, if weather permits. Small communities in Alaska may be visited by a state public health nurse two to four times a year and by an ANHS physician once or twice a year, but it is the Community Health Aide who provides the primary medical care and the emergency care for villages 365 days and nights of the year.

Community Health Aides bring together the benefits of training in modern medicine with an intimate understanding of their community and culture. They provide critical communications links between Western health care providers and their Native patients. Often they act as interpreters, not only of the language, but also of the problems that the persons in their villages experience. Thus, Community Health Aides serve an important role as mediators between two cultures, an intersection in the crossroads of cross-cultural health care.

Integration of Health Care Systems

With the emergence of the regional nonprofit corporations, some of the programs formerly under the direct management of ANHS have been transferred to these locally controlled organizations. Nevertheless, ANHS has control of the budget and thereby influences the

programs.[27] To comply with contracting requirements, the regional nonprofit corporations have evolved into bureaucracies that to some extent mirror the ANHS.[27]

While organizational integration can be accomplished contractually, making the services of the regional nonprofit corporations function in an integrated manner with ANHS is dependent to a great extent on the mutual respect and cooperation of the persons who work in each of the organizations. A crucial component is an effective referral network that assures that patients are seen by the most appropriate practitioner. Observing interactions between physicians at the ANHS hospital in Kotzebue and Native healers in Maniilaq's Eskimo Tribal Doctor's program, Juul commented, "I did not observe any contention or competition. . . . They work together to provide the best health care possible for their patients."[6(p68)]

The changing emphasis in the role of ANHS from a direct provider of services to contracting office has been demoralizing to some health care providers who have dedicated their entire professional careers to the Alaska program and "have a large emotional equity in what has been accomplished."[1(p41)] Fortuine summarizes the perceived changes from the viewpoint of these dedicated career officers in ANHS:

> Most of all they are concerned that the system so laboriously evolved might become seriously fragmented and even dismantled. Some worry that what they find challenging in the program now might not be in evidence in the future, especially since many of the more dramatic health problems of the natives have now been brought under some measure of control. As Dr Emery Johnson, Director of the Indian Health Service, has said: 'We have done all the easy things."[1(p41)]

The difficult task that lies ahead is to reverse the escalating rates of behaviorally based mortality and morbidity by rebuilding the self-esteem, sense of belonging and cultural pride that have characterized the Native peoples of Alaska. The importance of the regional nonprofit corporation is not the replication of ANHS under local control, but rather the evolution of new institutional forms in the Native cultures. These new management systems are integrating traditional values of Native cultures with Western medicine, thus allowing Alaskan Native people to use the better aspects of each culture to regain control of their lives through the promotion of their own well-being.

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Native Healing in Alaska

Report From Serpentine Hot Springs

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Traditional Alaskan Native healing practices, specifically sweat bathing and hot springs bathing, have medical connotations in that they involve sociocultural factors important to practicing medicine among Alaskan Native people. At Serpentine Hot Springs in northwest Alaska, relief for arthritis, back pain, hip pain, headaches, skin rashes and other disorders was sought. The "treatment setting" was an informal bathhouse and bunkhouse and Eskimo tribal doctors and patients were assigned tasks related to healing. Continuity with traditional cultural patterns was achieved in several ways: meals tended to be traditional Eskimo fare, the predominant language spoken was Inupiaq and styles of interaction were Inupiat in character. All patients showed improvement. The experience reported herein is instructive for those seeking innovative approaches treating Native American groups.

The Alaskan Native population today exceeds 64,000, including Eskimo (Inupiat and Yupik), Aleut, Athabascan and Tlingit people. Before and during the Russian presence in Alaska in the late 1700s, the indigenous people depended on their knowledge of anatomy, herbal medicine and other healing practices for the maintenance of health. Laughlin describes the following healing practices among Aleuts before Russian contact:

> The essential facts with which we must deal are: the existence of surgical skill, including suturing, removal of stone points, amputation, ligation, opening of the abdominal cavity; acupuncture, including the use of both fixed points and those determined by the individual case; blood letting, both annual and occasional; considerable skill in delivery of malposed foetuses, breach [*sic*] deliveries, etc.; massage applied commonly and rigorously, more often by women; the use of herbal hotpacks, sometimes in the sweatbath; and the use of a variety of herbals.[1(p132)]

After the United States government purchased the territory of Alaska from Russia in 1867, Western-trained medical practitioners became an increasingly important source of health care, particularly in combatting epidemic diseases introduced to the indigenous population at contact. Simultaneously, shamanistic beliefs and practices were discouraged in favor of Christian beliefs. In the 1950s the US Indian Health Service built hospitals in rural areas of Alaska and the territorial government began sending public health nurses to Alaskan Native villages. Despite a growing dependence on Western-trained medical practitioners, some traditional Native healing arts persisted.

As Western medicine curbed infectious diseases and reduced infant mortality, behaviorally based health problems emerged as the leading causes of death and disability in Alaska. Today, violence—accidents, suicide, homicide, alcoholism—is the number one killer in Alaska and alcoholism is the number one health problem.[2] Health professionals and community leaders are looking beyond the Western-oriented health care delivery system for innovative solutions to these complex problems. Experiments integrating traditional Native healers into the health care delivery system have been initiated in Alaska, planting the seeds for a cultural revitalization of Native Alaskan healing arts.[3-9]

We describe the contemporary use of hot springs as a place for healing in an Eskimo social context. Our report introduces traditional Alaskan Native practices that have medical connotations and illustrates sociocultural factors that are important to practicing medicine among Alaskan Native people. The experience we

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relate is instructive for those seeking innovative approaches to treating Native American and ethnic groups.

History of Hot Springs and Sweat-Bath Use in Alaska

More than 120 natural hot springs have been identified in Alaska; however, very little information is available on the use of hot springs by Native peoples. A few archaeologic and historic mining sites near hot springs have been described.[10,11] One report indicates that Indians traveled hundreds of miles to use the springs.[11] Traditionally, the Tlingit Indians used hot springs in southeast Alaska for bathing.[11] Despite these reports there have been no direct observations published regarding Native use of hot springs in Alaska for bathing or healing.

Whereas the antiquity, geographic distribution and importance of sweat bathing vary between cultural groups, the use of dry heat and steam heat baths by Native Alaskan and Canadian peoples is well reported throughout the arctic and subarctic regions.[12-23] Sweat bathing, as Lantis noted among northern Alaskan Eskimos, "was both a common means of secular and ceremonial cleansing and also a social institution."[13(pp107-108)]

The southwest Alaskan Eskimo *kashim,* or ceremonial house, typifies the use of sweat baths among Alaskan Eskimos. The kashim was not only a dance house, but a workshop, sweathouse, eating place and often the sleeping place of the unmarried men.[13] Guests from neighboring villages attending festivals would also be housed there. As Lantis observed, "The kashim was a broad institution in Alaska Eskimo culture. Besides being the place in which almost all festivals were held, the kashim figured in many everyday aspects of Eskimo life."[13(p105)] Communal sweat baths were taken for ritual purification before, during and after ceremonies, even though they were not an integral part of the ceremonies themselves.[13] In the absence of ceremonial occasions, the sweat bath provided a social occasion that often included dancing, singing songs about ancestors and great events, telling stories and sometimes feasting.[13,23]

Sweat bathing in Alaska is reported to have ethnomedical connotations, including relief from rheumatism, arthritis and sore joints or limbs[8,9,16,20]; relief from colds or sinus infection[16]; relief from dry skin or insect bites[24]; reduction of psychological stress,[16] and enhancement of general well-being.[13,23]

> There is an additional aspect of bathing which is difficult to characterize; this is the intoxicating effect of extremely hot baths. Leaving the stifling steam room, one is sometimes lightheaded, lacks full coordination, and may not be able to speak plainly for a few minutes.[16(pp129-130)]

Marsh and Laughlin[14] found indications that Aleuts at one time practiced surgical procedures in the sweat baths.

Native populations in the northern forests had adequate wood resources for sweat bathing. In the arctic, however, sweat baths required the use of driftwood, a relatively scarce resource on the Alaskan tundra. In describing ceremonies on Nunivak Island, Lantis commented regarding the custom of a father celebrating the birth of his child by giving a sweat bath for the men: "Since driftwood was valuable and had to be bought from those who had some at the time, this did represent a small outlay of weath."[13(p49)] In a later work, Lantis noted that "Certainly, the tundra villages did not have enough fuel for the weekly bath that many villages in the Bethel area now expect."[15(pp38-39)] In contrast, hot springs represent an unlimited geothermal energy resource. Yet, few Native communities have been located at the site of hot springs. Factors such as the availability of fish and game and transportation corridors, such as rivers, were more important determinants of settlement location in the arctic than an abundance of heat.

Data that follow on the contemporary Eskimo uses of Serpentine Hot Springs suggest a commonality with sweat bathing. Both institutions are multipurpose, having social, hygienic and healing functions. In both the kashim and the hot springs, activities are segregated by sex. The body temperature is raised in a hot bath, a steam bath and a dry heat bath, presumably resulting in similar physiologic phenomena.

Serpentine Hot Springs Bathing

Located in a hidden river valley 160 km (by airplane) north of Nome on the Seward Peninsula in northwest Alaska, Serpentine Hot Springs takes its English name from either the Serpentine River into which flow the clear waters from Hot Springs Creek or from the dramatic boulders scattered like sentries on the ridgetops guarding the cul-de-sac valley below. The springs erupt in two hot pools about 795 m apart. Although the water does not taste noticeably mineralized,[25] it has a hydrogen sulfide odor and a high mineral content.

Iyat is the Eskimo name for Serpentine Hot Springs, which means "cooking pot" or "a site for cooking." The surface temperature of the water has been measured at 60°C to 77°C (140°F to 170°F) and the mean reservoir temperature has been calculated to be 132 ±12°C (270°F).[26] The name Iyat, however, apparently derives from the spiritual activities believed to have occurred at Serpentine Hot Springs, rather than the shape or heat of the spring (notes by William Sheppard, anthropologist, Cooperative Parks Studies Unit, University of Alaska, Fairbanks, from Hot Springs Session, 1980 Bering Straits Elders' Conference).

The history of the Serpentine Hot Springs is derived from a few published reports by geologists exploring the region at the turn of the century[25,27,28] and recent attempts to record oral traditions, most of which are unpublished. Although gold was present in the Serpentine River area, gold mining was not considered profitable there at the turn of the century.[28] Nevertheless, miners from the Seward Peninsula used the hot springs as a relatively warm place for wintering. The first white person reached the hot springs in May 1900, traveling by dog team with a group of Eskimo assistants.[27] By September 1901 there was a small settlement with

buildings and gardens that the prospectors called "Arctic Hot Springs."[25,27] About 1915 they built a cabin near the upper spring and a bathhouse over a bathing pool 3.0 to 3.7 m in diameter.[25]

Jack Ningeulook, an Inupiat Eskimo informant from Shishmaref born in 1903, told Sheppard (field notes of William Sheppard, 1979) that the first time he had visited Serpentine Hot Springs was in 1915. He was herding reindeer with his uncle in the region. According to this informant, the miners first started using the hot springs for healing purposes and later the Eskimos followed the miners' example and used it for their own healing. According to another Eskimo elder, when the Eskimos became Christians they were freed from the influences Eskimos had believed controlled the hot springs (unpublished report from Hot Springs Session at 1980 Bering Straits Elders' Conference).

Documented oral accounts of curative uses of Serpentine Hot Springs among the Eskimos extend only to 1929, when one man recalled a group from Kotzebue traveling by dog team to Serpentine Hot Springs (William Sheppard's notes from 1980 Bering Straits Elders' Conference). Sheppard records the following story told by Jack Ningeulook about events that took place in 1935:

> Jack's cousin in Espenberg was very sick and could not walk. He got in touch with Jack and asked him to take him to the hot springs. Jack took him to the hot springs in a reindeer sled drawn by four deer. His cousin stayed on the sled wrapped in a sleeping bag. It took a week to reach the hot springs. He and his cousin stayed at the hot springs four weeks—until they ran out of food. At the end of that period of time, his cousin could walk a little bit (Sheppard's field notes, 1979).

Other Eskimo elders recall the early use of Serpentine Hot Springs by people from Deering and Shishmaref (William Sheppard's notes from 1980 Bering Straits Elders' Conference). Currently people visit Serpentine Hot Springs throughout the year. Local people believe that the water is "stronger" and contains more minerals during the winter before it is diluted by melted snow (personal communication, Augie Hoffman, Project Manager, Traditional Health Program, Maniilaq Association, September 12, 1983). People from Shishmaref use the hot springs for recreational and medicinal purposes during the time of the year when there is adequate snow cover for travel by foot, sled or snow machine and sufficient daylight hours to facilitate travel (unpublished report by Laurel Bland for Cooperative Parks Studies Unit, University of Alaska, Fairbanks).

Recently Maniilaq, the Native nonprofit corporation for the Kotzebue area, has organized groups to travel to Serpentine Hot Springs. Under the leadership of well-known Eskimo practitioner Della Keats,[3-5] small groups of patients journey to Serpentine Hot Springs twice a year for several days of soaking, curing, teaching and socializing. In June 1981 one of us (S.K.), a WAMI medical student, was invited by Maniilaq to accompany one of these groups. His role as a participant-observer enabled him to gather data that are the basis for the following description of current uses of Serpentine Hot Springs.

Healing Experience at Serpentine Hot Springs

After the spring thaw, it is possible to land small airplanes on a packed-clay landing strip located on a hillside south of the springs. The 15 persons (seven male and eight female) who came to Serpentine Hot Springs in June 1981 under Maniilaq sponsorship chartered a small aircraft from Kotzebue to make four trips to transport persons and supplies for a week-long visit. Whereas some lived in Kotzebue, others lived in surrounding villages. Two participants came from as far away as Anchorage and the Yukon-Kuskokwim delta in southwest Alaska. All (except S.K.) were Eskimo and spoke either Inupiaq or Yupik as their first language, though all could also speak English. The group, ranging in age from 5 to 76 years, included three Eskimo healers (Della Keats, Andrew Skin and Evelyn Barr), 11 adults seeking relief from physical problems, one first-year medical student participant-observer and one young child.

Medical problems for which people sought cures at Serpentine Hot Springs included arthritis, back pain, hip pain, headaches, skin rashes, strained muscles and other problems. Several of the participants had multiple problems. Most of the participants had already sought assistance from other sources, including Western-trained physicians and Eskimo medical practitioners, as shown in the following narratives:

> G, a 70-year-old man, fell into an ice hole while fishing in February and hurt his hip. He went to hospital in an ambulance because he couldn't walk. The doctors gave him pills and sent him home. "I threw 'em away," G reported. "The white doctors spend no time with you, they just give you pills. I stopped going to see them at the hospital." Five months later his hip was still painful and he came to Serpentine Hot Springs.
>
> D, a 21-year-old woman, hurt her back while jumping on a trampoline one year before. She had attempted to do a flip on the trampoline and landed wrong. A few months later, she sought assistance from an Eskimo healer who let blood from her lower back, which eased her pain. She came to Serpentine Hot Springs expecting to have her lower back "poked" again; but the Eskimo medical practitioners at the Serpentine Hot Springs retreat do not treat lower back pain in that manner. In addition to using the hot water and a sweating regimen to heal her back, she said she used the spring water to help her sinuses, to soak her eye and to drink for improved health.

There are two buildings at Serpentine Hot Springs: a bunkhouse for eating and sleeping and the bathhouse which has a plank-lined pool. Water from the hot springs and from a cool creek flows into the pool through pipes, which regulates the temperature of the pool. Bath water is replaced continuously as the pool drains to the creek downstream.

The daily regimen at Serpentine Hot Springs organized during the healing program reported here is centered on bathing, eating and sleeping. Usually three baths are taken each day, the first often occurring before breakfast. Men and women bathe in separate groups. Sometimes the men go first and other times the women go first.

The first group to bathe adjusts the water temperature to be "comfortably hot." Protocol insists that each bather drink one-half to one cup of spring water from

the hot tap before entering the bath, thereby allowing an initial adjustment of the body to the hot water. This procedure is considered necessary to derive maximum healing benefits from the springs. Occasionally a Christian prayer is offered before entering the water. Bathers descend by stairs into the pool one at a time. They splash themselves with water to grow accustomed to the temperature and sink to a squatting or sitting position in the 1.1 m (3½ ft) deep water. Typically, bathers sit in a circle with their backs to the walls of the pool and engage in conversation in Inupiaq.

Baths last no longer than 20 minutes. The duration of the bath is prescribed by the Eskimo healers, who take blood pressures, measure body temperature using standard thermometers and evaluate the general health of their patients.[29] During the bath stretching and limbering exercises are done, including cycling in place, arm rotations and modified knee bends. An Eskimo healer of the same sex accompanies the bathers to treat aches and pains. Red and inflamed areas are rubbed firmly to assist circulation. Necks are manipulated by rubbing straightened fingers from the top to the bottom of the neck. Bathers submerge their heads opening their eyes underwater as a soothing eye wash. Often the taps are adjusted to continually warm the pool until a temperature is achieved that can be withstood only by keeping perfectly still.

After 20 minutes, bathers ascend the stairs, dry themselves, dress and walk back to the bunkhouse where they get into their sleeping bags or bed rolls to sweat and nap for about an hour. Tang or fruit juice is drunk to replace liquids lost by sweating. Often each group (men or women) prepares the juice while the other group is resting. Meals are prepared and served after the hour-long rest has ended. Women prepare most of the food, which includes traditional Eskimo fare, such as dried reindeer, *ugruk* (bearded seal), seal oil and fireweed tops, as well as groceries from Kotzebue.

When not bathing, eating or sleeping, the participants at this hot springs healing program engage in group activities. They exercise, tell stories, play cards, hunt and make repairs or improvements to the bunkhouse. There is time for the Eskimo medical practitioners to teach each other new techniques as they diagnose and treat their patients who have come to the hot springs. They use traditional Eskimo healing techniques, which have been described elsewhere.[4,6,7] Depending on the illness, treatment may include *ilusiig,* manipulation of the abdomen to diagnose and treat internal problems. In addition, natural resources associated with the hot springs are used for medical treatments. A form of algae found in rivulets near the hot springs is used as a poultice for cuts and infections. After algae are applied, the skin may be wrapped with a plastic bag. Occasionally, the algae are mixed with seal oil, which is known to have a high vitamin A content.

Efficacy of Treatment

Although it is difficult to determine efficacy of treatment by such a small sample, observations of changes in patients' behavior and self-reporting by patients of improvement in their conditions during the week at Serpentine Hot Springs indicated pronounced improvement in half the patients and some improvement in all cases for which there were data. In no case was the physical condition complicated or exacerbated by the hot springs treatment.

Efficacy of the treatment at Serpentine Hot Springs may be attributed to some or all of the following factors: The therapeutic value of the heat or of the minerals in the water, the therapeutic value of associated traditional healing techniques including exercise, massage, manipulation of joints and other practices and the therapeutic value of the psychosocial experience. This last factor merits particular attention here.

The psychosocial experiences of participants at Serpentine Hot Springs involved a complex set of conditions that were characterized by cultural, social and spiritual attributes. The cultural heritage of all but one of the group members was Inupiat (northwest Alaskan) Eskimo, while the other was Yupik (southwest Alaskan) Eskimo. The predominance of Inupiat people in the group created a social situation in which the predominant language was Inupiaq and styles of interaction, as in joking and laughing, were Inupiat in character. The Inupiat culture was also manifest in some of the food that was prepared and eaten.

Participants at this Serpentine Hot Springs healing pilgrimage were removed from their families and their villages for the duration of the treatment program. Yet, they created a warm, supportive social environment for one another. The group spanned several generations. One of the healers brought along her 5-year-old great-grandchild who served the important function of creating a social environment similar to that in Eskimo homes where children are highly valued. Thus the composition of the group was somewhat similar to that of an extended family and seemed to stimulate mutual support. Separation of the sexes for sleeping and bathing created a camaraderie within the sex-based subgroups that may have been intensified by the intimacy of the situation. Group activities, such as bathing, cooking and eating, provided continual opportunities for interaction so that no one was isolated socially at Serpentine Hot Springs.

All of the healing activities were conducted with the assistance and support of the group. Not only the Eskimo medical practitioners, but also other members of the group were assigned tasks related to healing, such as holding a shoulder or leg of a patient whose joints were being manipulated. Participants took an active interest in the physical problems and healing of other members of the group, but they were asked to maintain confidentiality about the illnesses of others when they returned to their villages.

The spiritual component of the psychosocial experience was both formal and inherent. The formal component included prayers offered by persons before entering the pool of hot water and by healers before practicing a particular curing technique. Sunday is always the last full day at Serpentine Hot Springs for the

Maniilaq group, and a religious service is held in the bunkhouse. Each person individually makes a speech in Inupiaq giving thanks for their experiences and improved physical conditions at Serpentine Hot Springs. While prayers were offered in the Inupiaq language, they were typically Christian in content.

The sheer beauty of the Serpentine Hot Springs setting evokes a spiritual response. The rock formations surrounding the valley create an environment that stimulated people to think about powers greater than their own. Spirituality inherent in the aesthetic environment was enhanced by the relaxation and light-headedness brought about by the hot baths. These spiritual components in combination with the supportive social environment produced a transcendental experience for the participants.

Discussion

Evidence suggests that the therapeutic value of hot springs use by the Maniilaq group is enhanced by the interplay of cultural, social and spiritual components. Simple heat treatments or whirlpool therapy lacks this important context: an informal setting, group participation and continuity with traditional cultural patterns. This interplay between the content and context of healing reflects the importance of cultural revitalization to the spirit of the Native people of northwest Alaska. Programs like that sponsored by Maniilaq at Serpentine Hot Springs provide an opportunity for Western-trained physicians to refer patients for physical therapy in a context that is culturally appropriate and meets their psychosocial needs.

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Cultural Variation—Nutritional and Clinical Implications

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Cultural variation may play an important role in human nutrition and must be considered in either clinical or public health intervention particularly in areas with large immigrant populations. Acculturative and environmental change influence the food habits and health of transitional groups. Nutritional assessment may be complicated by cultural variation. The relationship between ethnicity and nutrition may be of evolutionary significance. Food beliefs may have beneficial or detrimental effects on health status. The study of acculturating populations may elucidate the pathogenesis of nutrition-related chronic diseases. Appreciation of the interaction of culture and nutrition may be of benefit to physicians and nutritionists in clinical practice and to those concerned with the prevention of nutrition-related chronic diseases.

Cultural variation plays an important role in human nutrition and must be considered in either clinical or public health intervention. A large body of literature is now available concerned with the food beliefs and practices of many different cultural groups. This literature ranges from participant-observation studies in small preindustrial societies newly exposed to Western cultures to large epidemiological surveys in highly developed countries. Because of the potentially confounding effects of political, economic and individual variation, and because of the complexity of nutritional assessment, it has been difficult to evaluate the interrelationship of nutritional status and cultural influences. Many recent investigations have sought to elucidate the nutritional importance of culture by focusing on populations in the process of acculturation. The significance of studying nutrition in transitional cultures has attained increased importance in the past decade, as the number of recent immigrants to the United States is greater than at any time in the past half century.[1] This influx has resulted in a drastic alteration in the demographic profile of communities, particularly in California, with Asian and Hispanic Americans representing the fastest growing segments of that population.[2] Additionally, these immigration patterns may be perceived as having shifted large populations from marginally industrialized to technologically advanced regions. Since these immigrants are mostly young and will be characterized by a birthrate much higher than the American mean,[1] it is likely that we will encounter many of the maternal and child health problems associated with less developed countries, including nutritional deficiencies, anemia, chronic infection and intestinal parasitism.[2] Culturally determined beliefs and practices regarding food use and health must be considered in the promotion of any form of intervention.

The food practices of a transitional group are subject to pressures for change which may be of two types; environmental and acculturative. There is evidence that food habits may be appropriate in a particular environment yet may lead to nutritional deficiencies or disease under different conditions. Or, food habits may be altered in response to "demands" for acculturation; such changes may either improve or worsen the nutritional quality of the diet and may be of importance in the epidemiology of several chronic diseases including dental caries, coronary artery disease, adult onset diabetes mellitus and hypertension. By studying the relationship between changes in food habits and alteration in the prevalence of such diseases, it is possible to describe

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more clearly their natural history and to formulate tentative suggestions for their prevention.

In this paper we will discuss general patterns of relationships between cultural beliefs and practices and nutritional health. We will describe differences in food habits and their impact on nutritional assessment and status, note illustrative nutrition-related diseases and their association with particular food practices in situations of environmental and cultural change, and examine strategies for prevention and treatment of nutritional disease.

Nutritional Assessment

The measurement of food intake and nutritional assessment are complicated by cultural variation. Jerome and Pelto[3] have highlighted the nutritional importance of a number of culturally determined variables including frequency of meals eaten away from home, form and content of occasional ceremonial meals and the degree of regularity of consumption patterns. Because of these factors the potential inaccuracies of standard clinical and research methods such as 24-hour dietary recalls or three-day food records becomes obvious. For instance, among low income urban black families in the United States, elaborate weekend meals are very different from those of the rest of the week and provide a substantial portion of total nutrients.[4] In addition, cultural groups may have concepts of what constitutes a food that are very different from those of nutritionists. For example, in Latin America, wild greens are rarely listed in food records although they may be an important source of vitamins.[5] Another source of measurement error is the use of dietary handbooks, whose nutritional tables are largely based on Western diets.[6] Thus, among Vietnamese immigrants to England it had been noted that, although calcium stores seemed adequate, the dietary intake of calcium was very low with almost no consumption of dairy products. Biochemical studies have indicated significant calcium supplies from dietary sources not usually considered, including pork bones and shells.[7]

Nutritional assessment is sometimes affected by ethnicity *per se* even when dietary intake does not appear to vary. Ethnicity may be associated with historical isolation sufficient to have permitted biologic evolutionary changes resulting in unique nutritional needs. For instance, Young and Scrimshaw[8,9] have noted marked differences in urinary nitrogen excretion in healthy Taiwanese and American college students fed similar protein-free diets. The Taiwanese conserved protein whereas the Americans had urinary excretion of nitrogen.

A number of studies have demonstrated an evolutionary pattern linking long-term use of dairy products by a group to the capability for digestion of lactose after early childhood, a feature that is unusual in non-pastoral populations derived from a non-pastoral background. This pattern is rather strikingly repeated throughout the world.[10] A good deal of current interest is focused on the effects of introducing simple carbohydrates into cultures that have not traditionally used them. Preliminary investigations have demonstrated that Eskimo groups, who satisfied their carbohydrate needs by gluconeogenesis of amino acids in association with a diet almost entirely based on meat and fish, have a very high prevalence of sucrose intolerance.[10] It has been suggested that the high prevalence of sucrase deficiency may account for the high prevalence of diarrhea noted in Eskimo infants in rapidly acculturating communities.[12] Although the above relationships are not fully documented, they suggest the inappropriateness of applying universal standards of nutritional needs. The same difficulties are associated with functional measures of nutrition, particularly growth. A number of investigators have suggested that ethnically specific standards for growth be used in recognition of the importance of biological variation between ethnic groups.[13]

Other investigators have highlighted the phenomena of catch-up growth and secular change, by which cultural and socioeconomic changes may dramatically alter growth patterns.[14,15] Conversely, rapid acculturational change and dietary transition may destabilize nutritional status, as suggested by studies of Southeast Asian refugee children in the United States.[2] In this population, it was found that hemoglobin levels were relatively normal upon arrival in the United States and then declined for several weeks before returning to normal. A final and perhaps insurmountable difficulty may be demonstrated in the many attempts to relate nutritional status to intellectual performance. Here, the confounding effects of cultural variation are particularly important.

Food Beliefs

One of the most striking characteristics of food beliefs, in most cultures, is the degree to which they associate with particular stages of the life cycle, notably pregnancy and the postpartum period for mother and infant. The humoral concepts that dominate the traditional medical systems of Latin America and Asia are amply shown in dietary prescriptions and prohibitions surrounding childbirth and child rearing.[16,17] Particular foods are assigned opposing qualities such as hot and cold, tonic and nontonic. Foods in each category are considered hazardous or beneficial depending on the setting. For instance, among Chinese families in San Francisco, infants are allowed only *neutral* foods, thus excluding most fruits and vegetables.[18] The nutritional consequences of such practices are controversial. Some have suggested that humoral nutritional beliefs reflect *folk* appreciation of health and disease.

Among Puerto Rican women it has been observed that those women who followed traditional food taboos consumed more vitamin rich foods and fewer simple carbohydrates and saturated fats than did women who consumed generally traditional diets without observing dietary restrictions.[19] On the other hand, nutritional surveys of Mexican-American primigravida women following humoral food beliefs have shown a number

of nutritional deficiencies despite apparently adequate availability of foods containing these nutrients.[20] In evaluating the benefits or liabilities of such traditional practices, there may be important nonnutritional considerations, particularly the role of food beliefs in maintaining cultural identity. Matthews and Manderson showed that many of the Vietnamese women whom they studied in Australia blamed a wide variety of subsequent minor ailments on their inability to follow certain traditional food practices during the postpartum period in the hospital.[17]

While food taboos may be the most obvious manifestation of cultural determinants of nutritional practices of pregnant women, more subtle beliefs may significantly affect the health of both mother and fetus, particularly with regard to inadequate or excessive weight gain and to the use or nonuse of supplements. In less developed countries and among a variety of disadvantaged groups in Western countries, the most serious health problems of infants are likely to arise from the combined effect of malnutrition and infectious diseases, particularly diarrhea and respiratory tract infections.[21,22] Although there are a number of political and economic obstacles that may hinder attempts to break this cycle, it has become increasingly clear that sociocultural factors may play an important part in the exacerbation of these diseases. Recent investigations have strongly suggested the importance of immediate rehydration and feeding in most childhood infections.[22,23] In many cultures, however, there is a prohibition against feeding sick children their normal diet, and few public health programs have been successful in attempts to modify such traditional practices (D. Echenberg, MD, PhD, unpublished data).

Cultural and Biological Interaction

The study of groups in cultural and environmental transition, particularly migrants, may illuminate the interaction of cultural and biological influences on food habits and nutritional status. The recent epidemic of rickets among the Indopakistani community in the United Kingdom provides an illustration of how such interactions may occur.

Rickets was a common childhood disease of the Industrial Revolution, with heavy smoke and dense housing combining to block sunlight and thus interfere with the critical step in the vitamin D pathway.[24] With the discovery of vitamin D early in this century, and the subsequent fortification of staple foods in most developed nations, rickets soon ceased to be a public health problem.[24] Beginning in the 1960s many cases of rickets were reported among new Indian immigrants in urban areas of Britain. In some areas it was estimated that a 5-year-old Indian child has a 4% to 5% likelihood of hospital admission with rickets before age 16.[25] Although the epidemiological picture is not quite complete, it now appears that the following scenario explains this epidemic. It was soon determined that "Asian rickets" was associated with residence in the UK and that return to the tropics resulted in increased vitamin D levels in this population, thus suggesting the importance of decreased exposure to irradiation in the pathogenesis of the disease. However, the absence of rickets among West Indian immigrant children suggests a culturally specific factor.[26] It is significant that West Indians use margarine fortified with vitamin D, while most Indians continue to use unfortified *ghee,* or clarified butter. In addition, the *chapatti,* a staple bread of the Indian communities, is known to have a high concentration of phytate which may decrease calcium absorption in the small intestine.[26] Vitamin D levels have had a strong negative correlation with *chapatti* consumption in this population.[27]

The "Asian rickets" epidemic may be viewed as a threshold phenomenon; alone, neither the low levels of sunshine in the UK, nor a diet low in vitamin D and high in phytate in India, would have been sufficient to produce the disease. Consequently, it is possible to assert that a dietary pattern well suited to the demands of one environment may become maladaptive in another setting. Viewed in evolutionary terms, it is possible to see such a situation as a source of selective pressures promoting either biological or cultural change.

Just as environmental change may make cultural food practices maladaptive, so cultural changes may lead to nutritional deficiencies within an otherwise unchanging environment. The nutritional implications of such cultural changes are exemplified by the process of Sanskritization in India, by which low caste forest tribes adopt the rituals, dress and diet of higher caste groups in an attempt to increase their status. Golpades and co-workers[28] have shown that this process of abandoning traditional diets, including forest fruits and animal foods, has been associated with increasing incidence of vitamin A and C dificiencies, and with nutritional anemias.

Acculturational Dietary Change

The investigation of food habits and cultural change has perhaps been most significant in providing a large portion of the enormous literature devoted to the associations between diet and the major chronic diseases of developed nations. A number of studies have promoted a general picture implicating the shift by acculturating populations to long-term consumption of diets high in saturated fats and simple carbohydrates in the increase in prevalence of one or more of these pathologic entities. Such changes in prevalence have usually followed a consistent pattern with respect to broad changes within a culture.

The investigation of acculturational dietary change has figured prominently in the attempts to elucidate the pathogenesis of the chronic diseases that have preoccupied epidemiologists for the past two decades, such as coronary artery disease and hypertension. The information gathered in these studies has had a strong impact on nutrition and health policy decisions in a number of countries, including the United States.[29] Although there is still a good deal of controversy regarding the role of acculturative changes in pathogenic processes, the strength of the evidence for the significance of cultural

food ways can be shown through two illustrations: (1) dental caries and (2) obesity and non-insulin dependent diabetes mellitus.

Dental Caries

Dental caries provide a good illustration of the relationship between acculturative change and health for three reasons. First, the role of diet in the development of dental caries is well documented. Recent reviews have confirmed the predominant pathogenic role of sugar intake.[30] Second, as the lag-time between exposure to cariogenic influences and the appearance of clinical disease is short, it is possible to examine changes in incidence in relation to short-term cultural or environmental changes, such as water fluoridation. Finally, the emergence of unprecedented levels of dental caries is one of the most evident public health consequences of the spread of Western culture and dietary habits.

Eskimos of Alaska and Northern Canada provide a particularly good illustration of this situation. Until recently, most Eskimos subsisted on an almost exclusively carnivorous diet with natural fluoride being provided through the consumption of marine mammals.[31] Early nutritional surveys reported a virtual absence of dental disease among Eskimos.[32,33] As the subsistence pattern changed from one of hunting and gathering to one of low-wage manual labor, the traditional diet was replaced by imported staples, primarily sugar, cereals and packaged foods purchased in trading posts. Currently, many Eskimo communities have perhaps the highest per capita sugar consumption in the world. There appears to be a strong relationship between the velocity of acculturation and the extent and pattern of dental caries.

Schaefer and his colleagues have investigated dental caries in two Eskimo villages.[31] In Inuvik, in the relatively developed western Arctic, there is a high prevalence of caries and missing teeth among middle-aged adults while the children of Inuvik, whose water is now fluoridated and who have access to preventive and clinical dental service have relatively good teeth. In contrast, in the Arctic Bay in the recently developed eastern Arctic, there is relatively little dental disease among adults of the same generation, but the children there, representing the first generation consuming an acculturated diet, have a high prevalence of dental disease.

Obesity and Non-insulin Dependent Diabetes Mellitus

Another striking consequence of the spread of Western culture has been massive weight gain in certain populations. Pacific Islanders and particular groups of Native Americans have been especially prone to the development of obesity. Although there is some evidence of genetic susceptibility in these populations, it has become progressively clear, through ethnographic and epidemiological studies, that a more important factor is a cultural tendency to weight gain resulting from increased availability of certain low cost foods. Investigations comparing migrants and nonmigrants or acculturated and nonacculturated members of the same population have shown a strong association between obesity and the adoption of Western dietary habits and sedentary life-style.[34,35] Dietary studies have described increased total caloric consumption, increased fat and protein consumption and decreased consumption of complex carbohydrates in a number of acculturating Pacific Island populations.[36] Among Samoans there is a clear gradient of obesity between unacculturated populations in Western Samoa, moderately acculturated populations in American Samoa and Hawaii, and highly acculturated Samoan populations in California.[37] In this last group, as many as 50% of adults may be at or above the 95th percentile weight for age, by American standards, despite height for age in the 25th to 50th percentile range, making them among the most obese populations in the world.

It is difficult to establish the importance of "acculturative obesity" in increasing risk factors for most chronic diseases. It is becoming progressively clear, however, that obesity is highly correlated with an epidemic of non-insulin dependent diabetes mellitus in many acculturating populations. Few cases of diabetes were reported in non-Western populations until about 40 years ago.[38] Within the past 40 years the epidemiology of non-insulin dependent diabetes has become clearer by intensive investigation of selected high-risk populations, notably Pacific Islanders and the Pima-Papago Indians of the southwestern United States.[39,40]

It has been postulated that the sudden emergence of diabetes in these populations represents the expression of a "thrifty gene."[40] In other words, in times of famine a genetic predisposition to diabetes mellitus would be adaptive in terms of enhanced ability to store nutrients as adipose tissue and thus conserve energy resulting from excessive secretion of insulin. With "feasting" represented by conversion to Western food habits, populations with high frequencies of such a genotype would be characterized by the disadvantageous appearance of clinical diabetes. Although the "thrifty gene" theory is supported by the extreme variance of diabetes prevalence in different ethnic populations, it is not clear why those groups with exceptionally high prevalence, such as the Pima-Papago, should have been subjected to greater selective pressures than other groups experiencing similar environmental conditions.

It has been noted that many groups with a rapidly rising incidence of diabetes have undergone particularly rapid cultural change. For instance, in Micronesia, the rate of development and acculturation increased rapidly as a result of phosphate discoveries on the island of Nauru. Consequently, per capita ownership of cars and speed boats became very high and the requirements for physical activity dropped substantially.[36] Dietary surveys have indicated extremely high caloric intake and frequent consumption of highly refined carbohydrates and alcohol; the traditional meal pattern has been displaced by one of irregular snacking throughout the day. The diabetes prevalence in these people of about 40% is among the highest in the world and is substantially

greater than in other Pacific Island populations with less westernized life-style.[35]

Patterns of Pathogenicity

Dental caries and adult onset diabetes mellitus represent two different patterns of pathogenicity associated with acculturative dietary change; for dental caries there appears to be a direct relationship between the introduction of large amounts of simple sugars into the diet and the appearance of disease. For diabetes there is a more complex association between diet and disease with several possible mediators including morbid obesity and genetic predisposition. Most of the other chronic diseases that have been linked with acculturation and dietary change exhibit equally individual epidemiological characteristics. For instance the increased prevalence of coronary heart disease among Japanese in California, in comparison with those in Hawaii and Japan, may be associated not only with the adoption of American dietary habits but also with the development of American social and work habits.[41]

Other diseases that have been extensively studied by nutritional epidemiologists and anthropologists include gastrointestinal tract malignancies,[42] hypertension[43] and gallbladder disease.[44] The beneficial effects of dietary change have been less popular subjects of investigation but are exemplified, perhaps, by the phenomena of catch-up growth and secular change, mentioned earlier.

Conclusion

From the examples discussed in this article, several practical points may be considered in attempting to include recognition of the importance of cultural variation in clinical and public health interventions.

In clinical settings, nutritionists could better evaluate dietary intake if they had access to nutritional handbooks that include non-American foods and could conduct more meaningful nutritional assessment and counseling by taking into account the ethnic differences in nutritional requirements and food habits. The evaluation of obese children or those suspected of failure to thrive would be more straightforward if ethnically specified growth charts were available, particularly in areas with large immigrant communities. For instance, there would probably be less concern about the growth of a Pilipino child who is in the 3rd percentile for height-for-age by National Center for Health Statistics standards if it were known that the child was in the 50th percentile according to Pilipino growth curves.[45]

The greatest opportunities for using understanding of cultural variation to improve nutritional status is probably in the formulation of public policy and educational programs.

The recent decline of rickets among Asian children in Scotland and Northern England suggests the potential effectiveness of public health programs in improving nutrition in high-risk populations.[46] Programs in Scotland have concentrated on providing vitamin D supplements, while those in England have focused on incorporating vitamin D rich foods into the diet and increasing the amount of time spent outdoors.[46] In both places, nutritional benefit was obtained without change in the traditional deficient diet. It is particularly important to consider the vulnerability of immigrant and acculturating groups to dominant cultural influences that may cause them to abandon nutritionally beneficial traditional foods for the heavily advertised, though less nutritious, foods of the new environment.

The failure of health workers to recognize the acculturating power of Western dietary habits may have contributed to the spread of Western diseases such as diabetes, coronary heart disease and dental caries. Ironically, dietary beliefs closely linked to cultural identity may be difficult to counter, even if they are clearly nutritionally detrimental, as in the tendency of mothers to underfeed a sick infant. The point is, therefore, that we should not blindly encourage dietary habits simply because they are traditional, but that we should recognize the power of cultural influences in preventing or promoting nutritional health.

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A Teaching Framework for Cross-cultural Health Care

Application in Family Practice

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Significant demographic changes in patient populations have contributed to an increasing awareness of the impact of cultural diversity on the provision of health care. For this reason methods are being developed to improve the cultural sensitivity of persons responsible for giving health care to patients whose health beliefs may be at variance with biomedical models.

Building on methods of elicitation suggested in the literature, we have developed a set of guidelines within a framework called the LEARN model. Health care providers who have been exposed to this educational framework and have incorporated this model into the normal structure of the therapeutic encounter have been able to improve communication, heighten awareness of cultural issues in medical care and obtain better patient acceptance of treatment plans.

The emphasis of this teaching model is not on the dissemination of particular cultural information, though this too is helpful. The primary focus is rather on a suggested process for improved communication, which we see as the fundamental need in cross-cultural patient-physician interactions.

Health care providers are finding themselves dealing with increasingly diverse patient populations. Fueled by armed conflict, political unrest and economic instability, the influx of immigrants into the United States is prompting a structural shift in the demographic representation of minorities. The impact is especially acute in states like California, which are subject to secondary migration or relocation after preliminary resettlement. These migration patterns, in combination with reproductive patterns, set a trend that is predictive of what has been termed *minoritization*.

In addition to language and socioeconomic barriers recognized to stand between minority populations and the health care system,[1-3] there is an increasing awareness of the impact of diverse health and disease belief systems on the interaction of health care providers and patients of a different cultural heritage.[4-10]

Overcoming these obstacles is aided by the incorporation of new tools for cross-cultural communication.* At the Family Practice Residency at San Jose Health Center, we have begun to develop a set of guidelines for health care providers in a practice that serves a multicultural patient population. We have structured these guidelines around the following mnemonic:

Guidelines for Health Practitioners: LEARN

- **L** *Listen* with sympathy and understanding to the patient's perception of the problem
- **E** *Explain* your perceptions of the problem
- **A** *Acknowledge* and discuss the differences and similarities
- **R** *Recommend* treatment
- **N** *Negotiate* agreement

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It should be emphasized that the LEARN model is not intended to replace completely the normal structure of the medical interview. Rather, it is intended as a supplement to history taking. The difference in focus is between a patient's factual subjective report of onset and duration and characteristics of symptoms and a patient's theoretical explanation of the reasons for the problem.

Discussion of Guidelines

Listen. Interview techniques have been proposed that aid in elicitation of a patient's conception of the cause, process, duration and outcome of an illness as well as healing strategies and resources that the patient considers to be appropriate.[4,6] Understanding a patient's conceptualizations and preferences constitutes the first step. Questions such as, What do you feel may be causing your problem? How do you feel the illness is affecting you? and What do you feel might be of benefit? are examples of the shift in focus.

Explain. Explanation or communication of a "Western medicine" model is the next step. This may be a biomedical model but often the provider is making an educated guess, for example, that a patient's diarrhea is indeed due to an intestinal virus as opposed to toxins from contaminated food or psychosocial stress. In the primary care setting, treatment is frequently initiated without a definite diagnosis or biomedical model. However, it is critical to the success of the interaction that the care-giver have a strategy and that the strategy be conveyed to the patient.

Acknowledge. Acknowledgment of a patient's explanatory model occurs next or is integrated into the previous explanatory step. Based on an understanding of the explanatory models of both patient and provider, areas of agreement can be pointed out and potential conceptual conflicts understood and resolved. Resolution may involve bridging the conceptual gap between disparate belief systems. In many instances there is no therapeutic dilemma involved and a patient's own model can be incorporated into the system of care. If the provider feels that a patient's explanatory model and its consequences may have possible deleterious effects, such as a toxic medicinal substance, then an attempt must be made to market a more appropriate model leading to the next step. An example of a counterproductive explanatory model and resultant intervention is the consumption of pickle brine for hypertension—called "high blood" by some southern blacks. "High blood" is characterized by too much blood and treated by avoiding rich foods and consuming pickle brine, an "astringent" substance. The high sodium content of pickle brine would likely be deleterious in the face of blood pressure elevation.[10]

Recommend. Within the constraints imposed by a patient's and provider's explanatory models, a treatment plan can be developed. Patient involvement in the treatment plan is important. This step constitutes an extension of such an effort to include cultural parameters when appropriate culturally relevant approaches can be incorporated into the recommendation to enhance the acceptability of the treatment plan.

Negotiate. Negotiation is perhaps the key concept of the proposed LEARN model. It is necessary to understand a patient's perceptions and to communicate the provider's perspective so that a treatment plan can be developed and negotiated. There may be a variety of options from the biomedical, psychosocial or cultural approaches that could be appropriately applied. The final treatment plan should be an amalgamation resulting from a unique partnership in decision making between provider and patient. A patient can truly be involved in the instrumentation of recovery if the therapeutic process fits within the cultural framework of healing and health.

Application of Guidelines

To illustrate the application of the LEARN model, we have selected examples from the experiences of our staff and students. We have chosen a separate case to exemplify each concept of LEARN. Although all or most steps in the model are involved in every clinical encounter, the cases were chosen to best illustrate each concept specifically.

- *Listen*

A 28-year-old Vietnamese woman, a social work student, was first seen in the Family Practice Center in autumn of 1982 because of weight loss, mood swings, nervousness, sweaty palms and an increased number of bowel movements. She had lived in the United States for five years. Initially she volunteered that she had been extremely depressed ten years earlier and had once attempted suicide. She had an established diagnosis of retinitis pigmentosa and was legally blind. She was living with her mother and two siblings and was entering college to study social work. On initial examination there were findings consistent with retinitis pigmentosa. Lid lag was also noted. Initial laboratory studies elicited values consistent with mild hyperthyroidism and she was started on a regimen of propranolol hydrochloride taken orally.

She was seen regularly and had a constellation of symptoms including abdominal pain, mute attacks during which she could not open her mouth, twitching and palpitations. After taking propranolol she felt very fatigued and weak and had an episode of syncope after which she refused to take further medication. Additional symptoms developed including squeezing substernal chest pain. Repeat thyroid function testing was normal.

There was no apparent physical explanation for the symptoms and it was felt that she was suffering from anxiety and depression related to her disability and life stress. Supportive approaches were instituted with regular counseling visits. Relaxation training and a life journal were begun. The technique used for relaxation included both breathing exercises and visualization.

Shortly after these measures were instituted the patient presented in a very agitated state and said that

the pleasant visual images she attempted to conjure turned "dark and scary." She also related that a childhood diary had been taken from her by one of her sisters and that the contents had been ridiculed. This made it very difficult for her to keep the recommended life journal. At this time, with encouragement, she related some very important events in her childhood. When she was 8 to 10 years of age her affliction was felt by her family to be due to her possession by an evil spirit, and a healer was summoned. The attempt at exorcism failed and this was interpreted as a sign that her illness was a form of punishment for her transgressions in a past life. She was virtually locked away in a back room for several years before the events that led to her immigration.

She stated she no longer held this set of beliefs, but she continued to worry about whether she was a good person. Her physician agreed with her rejection of the ideas held by her family and suggested that her studies in social work and her commitment to help people were indeed evidence of her goodness and worth.

She moved out of her home to campus housing and has improved somewhat. She continues to visit the Family Practice Center for supportive care.

Cultural context. The medicoreligious beliefs of Vietnam derive from such a variety of sources that specification of exact religious context of the healing rituals of this patient's early life is difficult.

There have been historical interchanges of Ayurvedic medicine, with its roots in Galenic humoral pathology, influenced by Hinduism and Buddhism, especially in Southeast Asia.[11-16] Chinese medicine, which is more closely related to Confucian and Taoist religious philosophies, has made an additional contribution. More recent influences come from Catholicism and Western medicine. Local indigenous beliefs and practices also no doubt exert some influence.[17(pp xviii-xxix)]

Attribution of illness to possession by spirits or demons is consistent with all of these religious traditions (including Catholicism, at least historically). Whichever temple and priest or shaman the patient's family applied to for help, her status as a victim of a malevolent source would have been validated by successful exorcism. This would have been confirmed by the return of her eyes to normal appearance. Failure of repeated exorcistic rites to alleviate the symptoms led to the conclusion that her deviant appearance was a mystical mark, a sign of evil committed in a former life. This conclusion transformed her from victim to perpetrator. In a family whose members include all of the living, dead and as yet unborn, the final diagnosis shamed the family in perpetuity. This was the justification for confining the child in the house and restricting her social interactions. The family was, literally, attempting to hide their shame. The psychologic burden that this explanation placed on the patient resulted in somatization of complaints. Mental illness, which bears strong negative sanctions for similar reasons, would have constituted yet another mark against the family.

The patient migrated with her family to the United States when she was an adolescent. The process of acculturation and an alternative biomedical diagnosis provided a context for a change of attitudes and perception of self-worth. Although several people whom the patient had consulted over time (social workers and health care providers) had felt that there was a troubling "cultural component" in her medical history, the patient had never been able to discuss it fully. Careful probing and an open, nonjudgmental attitude on the part of the resident physician allowed the patient to divulge the complete background information and to acknowledge the lingering self-doubt these experiences had produced. She was then able to initiate steps for improvement such as removing herself from the family context, which produced continuing stress and reinforced a negative self-image, and continuing her studies in a helping profession, which confirmed her goodness.

- *Explain*

A 21-month-old Mexican-American male infant with recurrent onset of fever, runny nose and noisy breathing was brought to the clinic by his mother. The mother noted that the child had been sleeping restlessly and making sighing noises while asleep.

On physical examination, he was found to have edematous mucous membranes and mucoid nasal discharge consistent with an upper respiratory tract infection (URI).

The mother stated that she was very concerned because two months earlier the child had had a major motor seizure that she associated with a high fever. She felt that the seizure had precipitated *susto* (fright disease), as evidenced by the sighing and restlessness during sleep, and wanted a regimen to control fever and prevent a worsening of the child's *susto*.

The resident physician discussed upper respiratory tract infections and their effects on breathing. He suggested a decongestant for relief of symptoms. He also confirmed the relationship of fever to seizures and advised continued use of antipyretics. He demonstrated the use of sponge baths to reduce fever and emphasized the importance of fever control in preventing seizures. In addition, he suggested that the mother consult a *curandera* (folk healer) concerning her questions about *susto*. The patient has subsequently been seen for routine visits and has had no further seizures or other significant problems.

Cultural context. Susto is a Latin-American folk illness that is caused by fright.[18-22] The source or cause of fright might be anything from a simple startle response to an encounter with spirits. Children are particularly susceptible to *susto*. Symptoms vary widely, but the sighing and restlessness or poor sleep pattern exhibited by the patient are common manifestations. The mother's explanatory model for this case of *susto* was as follows:

URI→fever→seizures→*susto*→sleep disturbance

The provider was able to give a detailed biomedical explanation of that portion of the patient's explanatory

model to which it was applicable and to recommend consultation with a folk specialist for that portion that lay outside the purview of modern medicine.

- *Acknowledge*

A 25-year-old Vietnamese woman was seen for a routine prenatal examination. As part of her evaluation she had blood drawn for laboratory testing. Within the next few days she returned with a variety of symptoms including weakness, fatigue and coryza. She attributed this to having blood removed, feeling that removal of blood weakens the system and causes illness.

Her provider, a Vietnamese physician, was aware of the belief and acknowledged it, but also explained how much blood volume she actually had and gave the example of persons donating blood, a much larger volume, without symptoms.

She was pleased with the explanation, seemed to feel less fearful and her symptoms abated.

Cultural context. The probable influence of Chinese medicine or Ayurvedic medicine (or both) in Southeast Asia is seen in this patient's response to blood tests. Edwards[23] describes the following physiological process from Chinese medical theory: "The connection between food, [blood], sex and health is found in the transformational formula in which seven units of the precursor yields one unit of the subsequent product:

Food→blood→*jing*→*qi*→*shen*"

Edwards defines the terms as follows: *jing*="sexual fluid," which is a vital substance; *qi*="breath" or "life energy" (also written *chi*); *shen*="ethereal energy." A similar process has been described from Ayurvedic medical theory, which could be outlined as follows:

Food→chyle→blood→flesh→fat
bones→marrow→semen[24]

Because several physiological systems are involved in the production, transportation and storage process —that is, digestive, genitourinary, circulatory and respiratory—symptoms can be diffuse and varied. Since all descriptions indicate a geometric reduction between precursor and product, the consequences of interruption of the cycle would increase geometrically in seriousness at each earlier step in the process.

The patient's and the provider's explanatory models were similar in that they both believed blood loss to constitute a potential threat to health. Their explanations differed in the amount of blood that must be lost to pose a problem. By relating the amount of blood removed to the total blood volume and comparing this with the much larger quantities safely removed from blood donors, the physician was able to reassure the patient and to effect alleviation of symptoms.

- *Recommend*

A 38-year-old Mexican-American man was seen in the Family Practice Center for chronic genitourinary problems. He had experienced hematuria and right flank pain two years before. In addition there had been recurrent episodes over 18 years of right flank pain and dysuria, diagnosed as urinary tract infections. He did not use analgesics. Examination of the external genitalia and prostate was unremarkable. He had no abdominal or flank tenderness. Analysis of urine showed 50 to 100 leukocytes per high dry field. An intravenous pyelogram showed a localized hydronephrotic area in the upper pole of the right kidney.

He was seen by a urologist who carried out retrograde pyelograms. These showed a large calyceal diverticulum connected with the right collecting system, with hydronephrosis of the upper pole of the kidney.

Surgical treatment was recommended. The patient expressed considerable reluctance to have an operation. When questioned by his family physician he expressed concern that his "blood was low" and that he would have trouble going through an operation under the circumstances. His physician discussed the amount of blood that could be expected to be lost with a partial nephrectomy and also the total available blood supply in the body. He suggested that a surgical procedure be delayed for a period to allow the patient to "build up his blood" with appropriate medication. This was quite acceptable to the patient and the consultant urologist.

He subsequently underwent uneventful partial right nephrectomy.

Cultural context. Blood is "hot" according to the hot-cold system of humoral pathology as practiced in Latin America. Blood is also associated with strength, both in the health and the sexual sense. Having a large supply of blood makes one strong and healthy, but is also associated with virility and hence with machismo. Menstrual blood, semen and sexual activity are very hot.[25] Men's blood is hotter than women's blood.

The patient felt a need to build up his blood supply in order to have reserve strength for an operation because he expected a significant amount of blood to be lost during it. He was willing to accept the recommendation that he take iron to help build blood. However, an equally acceptable way to build blood would have been to eat blood products such as fried blood or blood sausage. Organ meats are good for building up strength and blood supply. In the Mexican-American folk system, an abundant and varied diet builds physical reserves, including a healthy supply of blood.

By describing the surgical procedure, including control of bleeding, the resident physician was able to alleviate some of the patient's concerns about blood loss. The provider was then able to recommend a treatment plan acceptable to the patient by prescribing "blood building" medicines and by scheduling the operation following a delay of fixed duration that the patient concurred would be adequate to prepare himself.

- *Negotiate*

A 48-year-old black man was seen because of severe hypertension and congestive heart failure associated

with far-advanced renal insufficiency. Initially he was managed conservatively. It became obvious, however, that he had reached a stage at which renal dialysis was his only hope for survival.

When he was approached about the possibility of hemodialysis he declined, stating that he was a devout Christian and felt that the will of God was of prime importance and that he would wait for God's intervention rather than accept dialysis.

His physician acknowledged the importance of God's influence, but suggested that the opportunity for dialysis as a means to control his condition might be the way God had intended for him to survive. Indeed, there was nothing in the Bible that prohibited dialysis and God helps those who help themselves.

The following day the patient consented to hemodialysis and now has a functioning bovine shunt and is doing well.

Cultural context. The socioreligious context of this patient's explanatory model was fundamentalist Protestantism. The direct intervention and control of health by God is supported in the Old Testament (Exodus 4:11): ". . . who maketh the dumb or deaf, or the seeing or the blind? Have not I the Lord?" The New Testament contains dozens of examples of the healing powers of Christ.[26] While one common alternative to treatment is faith healing,[27] this patient seemed to be relying on the Old Testament with healing based on direct intervention by God. He suggested that he felt that God did not intend him to die yet and would intervene on his behalf. The provider was able to call on other aspects of Christian beliefs such as "the Lord helps those who help themselves" and that God sometimes works through human agents: "For to one is given by the Spirit the word of wisdom; . . . to another the gift of healing by the same Spirit" (I Corinthians 12:8-9).

The implication was drawn that the physicians and dialysis might be the instruments through which God intended to intervene. Medical intervention was thus translated into a construct that did not violate the tenets of the patient's faith. By using beliefs from the patient's own religious background, the provider was able to negotiate acceptance of recommended biomedical treatment.

Summary and Conclusions

Given current demographic trends it is probably unrealistic to assume that health care providers can gain in-depth knowledge about the health-affecting beliefs and practices of every ethnic or cultural group they are likely to encounter in practice. The processes of acculturation, interethnic variation and social change also serve as confounding agents in predicting knowledge, behavior and attitudes. Social class differences, too, provide striking variability. We have, therefore, chosen a process-oriented model by which the cultural, social and personal information relevant to a given illness episode can be elicited, discussed and negotiated or incorporated.

However, it is common in our experience for patients of different beliefs to be reluctant to discuss this problem for fear of criticism or ridicule. It is certainly of value for providers who deal with culturally diverse patients to have some understanding of common basic conceptions of health, illness and anatomy held by these persons. Much work needs to be done in codifying these conceptions and making them available to professionals in medicine.

The foregoing examples serve to illustrate some of the means the members of a family practice residency program have used for enhancing communication and promoting the integration of patients' and providers' perceptions of needs and solutions into the therapeutic process.

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